The New England
Journal of Medicine

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Volume 251 DECEMBER 2, 1954 Number 23

PATENT DUCTUS ARTERIOSUS WITH REVERSAL OF FLOW*

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SHOULD closure of a patent ductus arteriosus with reversal of flow be attempted? If so, how can the high surgical mortality hitherto reported[1-3] be reduced? An attempt is made to answer these questions on the basis of a case of this syndrome in which records were available from the age of ten years to death during operation at the age of twenty-five.

CASE REPORT

In 1938 a 10-year-old girl came under the observation of Dr. Ernst Boas. We are indebted to him for the findings presented below. At the age of six months an enlarged heart had been found on x-ray examination. In February, 1938, after a sore throat, intermittent fever for several weeks was observed. The erythrocyte sedimentation rate was rapid, and leukocytosis was present. The first examination in April revealed "systolic and diastolic murmurs" in the pulmonary area. The pulmonic 2d sound was accentuated. The tip of the spleen was palpable. Fluoroscopic study showed a dilated pulmonary artery and moderate enlargement of the left and right ventricles. An electrocardiogram disclosed right-axis deviation. A diagnosis of probable patent ductus arteriosus was made and the possibility of subacute bacterial endocarditis considered, but a blood culture was negative. The fever subsided. In 1939 the diastolic murmur was no longer audible. An electrocardiogram showed no change from the year before. In 1943 the patient was able to ascend only 1 flight of stairs but danced freely. At that time no murmurs were heard.

She was admitted to the Mount Sinai Hospital for the first time in December, 1947, at the age of 19 years, because of hemoptysis, dyspnea and wheezing. There was no cyanosis or clubbing of the fingers. The blood pressure in the left arm was 105/90. No murmurs were noted although the pulmonic 2d sound was accentuated. On x-ray and fluoroscopic examination prominence of the pulmonary-artery segment and widening of the smaller vessels throughout the lung were apparent. An electrocardiogram suggested enlargement of the right ventricle. The hemoglobin varied from 17.0 to 18.7 gm. per 100 cc. Indirect laryngoscopy disclosed paralysis of the left vocal cord although the patient was not hoarse. Angiocardiographic examination was unsuccessful. The oxygen content in samples of blood removed from various chambers, as determined by cardiac catheterization is indicated in Table 1. The pulmonary artery was not entered and no pressures were obtained during this catheterization, but on the basis of the oxygen content of blood in the various chambers, no shunt could be postulated. The brachial-artery blood was normally saturated with oxygen.

In January, 1950, the patient was readmitted to the hospital because of increasing anxiety, exertional dyspnea and weakness. On this occasion faint cyanosis of the fingernails was noted. A transient systolic murmur was heard at the apex. The hemoglobin varied from 17 to 21 gm. per 100 cc., and the red-cell count was 6,800,000. The hematocrit was 64 per cent, and blood volume was increased (94 cc. per kilogram of body weight as determined with use of Evans blue dye). Brachial-artery blood (side not specified) was 92 per cent saturated with oxygen. During an exercise test, utilizing the Millikan ear oximeter, blood oxygen saturation fell from 92 to 85 per cent. Cardiac catheterization was performed under tribromoethanol anesthesia because of the patient's anxiety. No abnormal communications were demonstrated by the exploring catheter (Table 2).

The variations in oxygen content in the various chambers of the heart showed no consistent trend indicative of a shunt, and were explained as due to lack of a steady state. Severe hypertension in the right ventricle and pulmonary artery was established, and, although overriding of the aorta could not be proved, a tentative diagnosis of Eisenmenger's complex was made. The presence of peripheral arterial unsaturation contrasted with the previous findings, but it was not until later that it was realized that different arteries had been used.

After discharge from the hospital the patient experienced severe anxiety, and became addicted to barbiturates. In addition there were dizzy spells, increasing dyspnea on exertion, cyanosis, palpitation of the heart and pain in the anterior aspect of the chest radiating to the left shoulder.

In October, 1952, at 24 years of age, she was admitted to the hospital for the 3d time because of extreme apprehension and attacks of shortness of breath.

She was distinctly cyanotic, without clubbing. The left hand was more cyanotic than the right — a fact that she herself had noted. The toes, if anything, were less cyanotic than the hands. The blood pressure in the right arm was 100/85. The 2d sound at the apex was split, and the pulmonic 2d sound was also split and accentuated. There were no murmurs except in the pulmonary area, where a rough, medium-loud late systolic murmur was heard only during expiration. The hemoglobin was 18 gm. per 100 cc. X-ray examination of the chest (Fig. 1) showed no change from that taken in 1947. An electrocardiogram (Fig. 2) indicated hypertrophy of the right ventricle, with no major change from that taken by Dr. Boas 14 years previously.

Her activities while in the hospital were sharply limited, but it was difficult to tell what part her anxiety played in this. It was repeatedly observed that under conditions of the slightest mental distress she hyperventilated and became increasingly cyanotic. At times this was so severe that she momentarily lost consciousness, presumably from anoxia.

The fact that the cyanosis in the left hand was greater

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than that in the right fortified the growing suspicion of a patent ductus arteriosus with reversal of flow. When the record was reviewed, 2 other facts supported this assumption: Dr. Boas had heard a murmur suggestive of patent ductus at the age of 10, and the brachial-artery blood, in 1947 and 1950, had been fully saturated with oxygen, whereas femoral-artery blood, in 1950, had been unsaturated.

Angiocardiographic studies in the supine position were performed, under general anesthesia, at the New York Hospital.* The frontal projection was used. The superior vena cava and right atrium were not remarkable. The right ventricle was enlarged and extended almost to the left border of the heart. Simultaneously with the visualization of a dilated pulmonary artery (Fig. 3) the ductus arteriosus itself was filled with contrast medium. It was 10 mm. in diameter near its origin. In the same film, taken 1½ seconds after the injection, dense opacification of the descending aorta occurred. There was some opacification of the aortic arch and the right innominate and left brachiocephalic vessels, presumably by retrograde flow in the aorta. Neither the left atrium nor the left ventricle was opacified.

After the angiocardiogram, and while the patient was still under thiopental sodium anesthesia, blood was removed simultaneously from the right radial and femoral arteries.

TABLE 1. *Results of Cardiac Catheterization.*

SITE	OXYGEN CONTENT*
	vol. per cent
Coronary sinus	4.3
Superior vena cava	18.2
Right atrium	18.0
Right ventricle	18.9
Brachial artery	24.4

*Oxygen capacity, 24.6 vol. per cent.

TABLE 2. *Oxygen Content and Saturation and Pressure in Various Chambers of the Heart.*

SITE	OXYGEN CONTENT	SATURATION	PRESSURE
	vol. per cent	%	*mm. Hg.*
Superior vena cava	16.6	73.6	0
Right atrium	15.3	67.8	1
Right ventricle (outflow)	16.9	75.0	97/4
Right ventricle (apex)	14.8	66.0	113/4
Main pulmonary artery	14.0	62.0	107/70
Right pulmonary artery	15.8	70.0	100/60
Right femoral artery	17.6	78.6	—
Capacity (oxygen)	23.1		

The oxygen content in the radial artery was 17.4 vol. per cent (71.9 per cent saturated), and that in the femoral 13.3 vol. per cent (54.9 per cent saturated).

The diagnosis of patent ductus arteriosus with reversal of flow having been established, operation was decided on but was delayed for 3 months because an unexplained fever (temperature of 100 to 100.5°F. daily) became manifest and did not recede with large doses of penicillin or streptomycin. During this period the patient was on the psychiatric service, where intensive psychotherapy helped prepare her for operation, which was undertaken on March 17, 1953.

Under basal tribromoethanol anesthesia, a double-lumen catheter was passed through the left brachial vein so as to lie with the tip in the main pulmonary artery and the proximal opening in the right ventricle. Pressure records and simultaneous electrocardiograms were made just before and during the surgical procedure by means of Statham pressure transducers and a specially built recorder.†

In the operating room cyanosis was striking and became intensified as anesthesia was deepened with ether. The blood pressure varied from 80 to 100 mm. of mercury systolic by palpation from this point on, and the cardiac rate remained between 140 and 150. Pressures in the pulmonary artery and right ventricle were 135 to 140 mm. of mercury systolic. It seemed unlikely that the patient would ever be in better condition, so the operation was undertaken.

With the patient on her right side the chest was entered through a long left posterolateral incision in the bed of the 4th rib. Numerous tortuous collateral vessels were found.

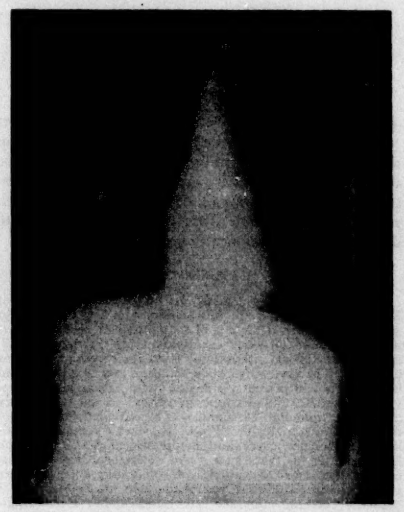

FIGURE 1. *X-Ray Film of the Chest (1952), Showing Prominent Pulmonary-Artery Segment and Increased Smaller Vascular Markings.*

Note that the transverse diameter of the heart is within normal limits.

The aorta was isolated proximal and distal to the ductus arteriosus, which appeared to be 1.5 cm. long and of the same width. The pulmonary artery was widely exposed with the pericardium open. During the dissection the heart rate gradually slowed, and the pressures in the pulmonary artery and right ventricle dropped progressively. Transient nodal rhythm occurred, and later progressive widening of the QRS complex, with bundle-branch-block pattern, appeared.

After the ductus had been completely isolated but before any attempt to ligate it was made, the heart action became very poor. As part of the attempt at resuscitation, it was decided to clamp the ductus, in the hope of relieving peripheral anoxia. However, the deterioration was not altered and ventricular tachycardia and fibrillation developed. Attempts at electric defibrillation and use of various drugs (procaine amide, epinephrine and calcium chloride) were of no avail.

During a period of ventricular tachycardia the pressures in the right ventricle were raised by cardiac massage from about 30/16 to a systolic of over 75 mm. of mercury. During the same period the pulmonary-artery pressures (maximum 27 and minimum 9 mm. of mercury) were raised during cardiac massage to 50/30.

*We are indebted to Drs. Israel Steinberg and William Dubilier, Jr., for performing the study and permitting us to report their findings and reproduce the films.

†Available from Electronics for Medicine, Incorporated, New York City.

The possibility that the cardiac catheter was responsible for the arrhythmias was rejected, and the instrument was therefore left in place.

At post-mortem examination* the heart was enlarged, weighing 400 gm. This enlargement was due chiefly to severe hypertrophy of the right ventricle. The ductus arteriosus was 2 cm. wide by 0.8 cm. long. It showed marked atherosclerosis, with a single transverse tear of the intima, at the site of application of the clamp during the resuscitative effort (Fig. 4).

By contrast, the aortic intima was smooth. There were no impingement plaques in the aorta or pulmonary artery. The foramen ovale was closed.

The mitral valve was thickened and shortened, suggesting old rheumatic inflammation both grossly and microscopically, but without evidence of rheumatic activity. Small subintimal hemorrhages were found on the anterior leaflet of the tricuspid valve and in the infundibulum of the right ventricle. These were attributed to trauma from the cardiac catheter.

The microscopical changes in the pulmonary arteries were of great interest and will probably form the basis of a separate report. Briefly, in addition to advanced atherosclerotic changes in the larger intrapulmonary arteries, the smaller ones, just beyond naked-eye visibility, showed extreme narrowing of their lumens, with intimal proliferation and fibrinoid deposits. When studied in serial sections these lesions could be followed to complete obliteration of the lumen accompanied by destructive medial alterations.

Distal to these occlusions one could find glomus-like formations communicating with pulmonary veins, thus constituting arteriovenous anastomoses, although continuity could not be established between the lumens of the arteries and veins.

A few of the arterioles contained multiple small vascular channels superficially resembling recanalized thrombi, but

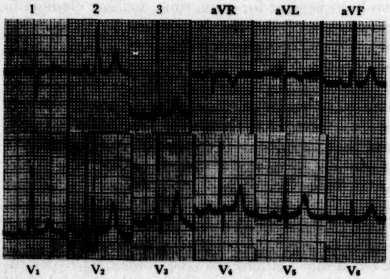

FIGURE 2. *Electrocardiogram Taken in 1953, Shortly before Operation (Standardization–1 Millivolt Equals 1 Cm.). The pattern of right-ventricle hypertrophy is evident.*

special stains in similar cases[4] have indicated that they may be unusual forms of arteriovenous communications.

DISCUSSION

This patient was observed from the age of ten, and in reviewing her history one may legitimately raise the question whether she had pulmonary hypertension with reversal of flow all during this period, or whether reversal of flow was an end stage in the natural history of the increasing pulmonary hypertension that may occur in any case of patent ductus arteriosus. Dammann, Berthrong and Bing[3] and Limon Lason et al.[5] describe patients with this syndrome who were cyanotic from birth. Although our patient had systolic and diastolic murmurs suggestive of patent ductus with usual flow when seen at the age of ten, it is not clear whether these were of typical "machinery" quality. The presence of electrocardiographic changes indicative of hypertrophy of the right ventricle at that age suggests that some degree of pulmonary hypertension was probably present very early in life.

It has been postulated[6] that the pulmonary hypertension in these cases may not result from the increased blood flow through the lungs, but that the resistance in the pulmonary circuit may fail to drop after birth; that the equality of pressures in the two ventricles characteristic of the fetus[7] persists into extra-uterine life; and that the ductus arteriosus fails to close. At present there is at best only scanty evidence to support this point of view.

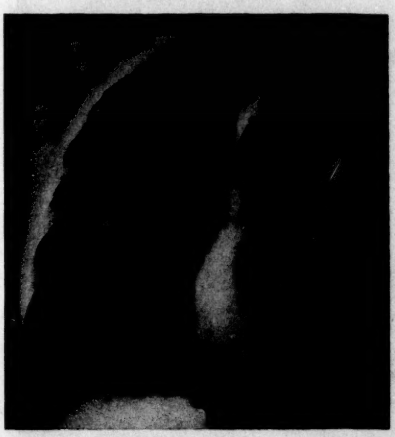

FIGURE 3. *Angiocardiogram Taken One and One-Half Seconds after Injection.*

Both main pulmonary arteries are filled. The shadow assumed to be the ductus arteriosus is visible as a tapering projection above the left pulmonary artery. The descending aorta is densely opacified, and there is a small amount of Urokon in the aortic arch. The right innominate and left brachiocephalic vessels were also opacified in the original films, but do not show in the reproduction.

It is impossible to state at what age the right-to-left shunt in our patient first began. However, at the age of twenty-two, when the femoral-artery blood was 78 per cent saturated with oxygen, only faint cyanosis was noted in the fingernails.

Observations in this as well as in other cases suggest the possibility that the unsaturation of the arterial blood may be due in part to pulmonary factors. Limon Lason et al.[5] report that in 1 of their cases with reversal of flow in which the ductus was successfully ligated, the pulmonary-artery systolic pressure fell approximately to half the preoperative level, but

*Performed through the chest wound by Dr. Bernard M. Wagner; Dr. Lotte Strauss reviewed the gross and microscopical specimens and performed serial-section studies of the lungs.

the unsaturation of arterial blood persisted at about the same level (72 per cent). Storstein and his associates[8] had a similar experience.

The distinctive differences in the arterial saturation between the upper and lower extremities on the one hand, and the left and right arms on the other, have been noted before.[9,10] The former may be difficult to evaluate clinically, whereas two hands are easier to compare, and in the case reported above the difference was striking. The course of the circulation was clearly depicted by angiocardiography.[11-13] Not only did the ductus itself become opacified but also the greater part of the contrast substance entered the descending aorta, with a smaller reflux into the left brachiocephalic vessels.

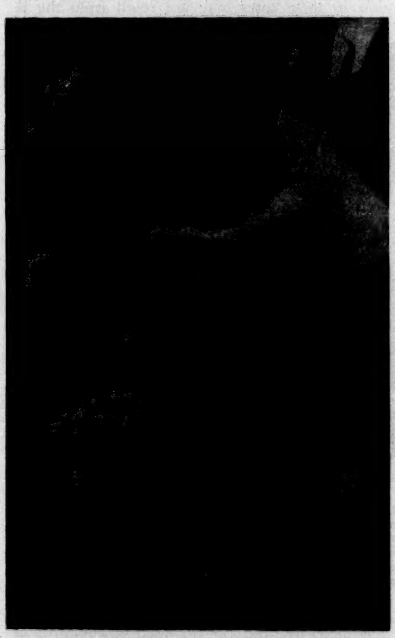

FIGURE 4. *Post-Mortem Photograph, Showing Atheromatous Changes in the Pulmonary Artery and Ductus Arteriosus, with a Relatively Smooth Aorta.*
The transverse tear in the ductus was presumably caused by application of the clamp during surgery. The specimen has been opened from the front.

The physiologic reactions to anxiety that occurred in our patient are of interest. The circle of anxiety, hyperventilation, increased cyanosis and increased anxiety occurred on many occasions and led, at least once, to transient unconsciousness, presumably from anoxia. It is understandable that the anxiety eventually came to dominate the clinical picture.

The ability of voluntary hyperventilation to increase the right-to-left shunt in tetralogy of Fallot and some cases of Eisenmenger's complex has been noted by van Lingen and Whidborne.[14] Hamilton, Winslow and Hamilton[15] reported a case of tetralogy of Fallot in which peripheral hypotension resulting from anxiety (or other stimuli) was associated with a drop in arterial oxygen saturation. The mechanism for both was considered by these authors to be a drop in peripheral resistance, the pulmonary resistance being unable to change. However, we do not completely discount the possibility that pulmonary resistance is raised in cases with pulmonary hypertension by violent expiratory effort.

The surgical aspect of this syndrome poses three problems. The first is the advisability of surgery in a given case. Secondly, if operation is decided upon, how may the patient best be handled on the operating table up to the time when the ductus is ligated? Finally, how may the ductus best be obliterated?

When there is reversal of flow in a patent ductus arteriosus, there are, as a necessary part of the picture, hypertension in the pulmonary artery and marked increase in pulmonary vascular resistance. When, owing to any one of a number of circumstances, increased pulmonary pressure and resistance have been present for some time, striking changes in the anatomy of the pulmonary vascular bed occur. These have been well documented in animals and in man in several different conditions.

It is interesting to speculate whether these changes would be reversible if the initiating cause of the pulmonary hypertension were withdrawn. There is evidence that the process is reversible in young children and possibly, after mitral commissurotomy, in young adults. Thus far, there is no evidence to indicate when it might be considered irreversible — particularly, how long it could be present before this would be true.

Even if one assumed that the pulmonary hypertension would persist after operation, there would still be, in our opinion, sufficient justification for surgery. We do not agree with the concept[3] that the patent ductus serves as a vent to the output of the right side of the heart in these cases. The right ventricle must eject sufficient blood to support the pulmonary blood flow and the ductus flow. If one could establish a state in which it would only have to support the former, it is difficult to see how this would be worse for the patient. It appears to be a problem only in adjustment during the acute phase when output of the right side of the heart is still large, and before the output and peripheral resistance of the left ventricle are sufficiently adjusted to support the aortic pressure.

When it has been decided that operation is advisable, the problem how best to manage the patient in the early stages of surgery and during the actual closure of the ductus remains. It is apparent that before ligation an effort should be made to control the relation between the pressures in the pulmonary artery

and the peripheral arteries in the hope of reducing the right-to-left shunt. During operation on our patient the systolic pressure in the pulmonary artery was higher than that in the peripheral arteries by a wide margin, and although neither oximeter studies nor direct analyses of arterial blood were performed, the marked cyanosis noted attested to the degree of peripheral anoxia that was present and probably contributed to the fatal outcome. The possible effect of straining during induction of anesthesia, and of positive pressure intratracheal anesthesia in raising the pulmonary resistance and increasing the right-to-left shunt, should be borne in mind.

The final problem, already touched on, is the adjustment of the circulation during the acute phase of ductus closure. The sudden complete occlusion of the ductus may be too much of a stress to be borne by the right ventricle. Glenn[16] has indicated that when he did this in a case of patent ductus with reversal of flow, the blood pressure fell precipitously and the heart did not tolerate it. He released the occlusion, with immediate good effect, and did not proceed with the closure.

It has been proposed[17] (and was considered in the case reported above) that the operation might be performed in two stages, creating an anastomosis between the subclavian and the pulmonary artery at the time of obliteration of the ductus arteriosus, and closing the new shunt at a later date.

In our patient, however, we were prepared to try to close the ductus slowly. We had introduced the cardiac catheter to serve as a guide to the speed of closure. A rise in the end-diastolic pressure in the right ventricle was the anticipated index of right-sided heart failure. If the pulmonary-artery pressure rose precipitously or peripheral arterial pressure dropped, we were prepared to slow down or stop and wait during the closure. Venous bleeding, the application of tourniquets and arterial transfusion were also considered to see us through the period of adjustment.

We did not have the opportunity of testing this point of view and do not believe that this case can be cited either to support or to deny the statement that a patent ductus with reversal of flow can be closed successfully. We shall try the same procedure if presented with the problem again.

Summary

A case of patent ductus arteriosus and reversal of flow in which observations were available from the age of ten to death during operation at the age of twenty-five is reported. The diagnosis was suspected on clinical grounds and established by cardiac catheterization, angiocardiography and differential arterial blood studies in the upper and lower extremities. We believe that closure of the ductus should be attempted in these cases. The principles by which the surgeon should be guided are suggested.

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THE CLINICAL EVALUATION OF PHENYLINDANDIONE AS AN ANTICOAGULANT*

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In 1944 indandione derivatives were reported by Kabat, Stohlman and Smith[1] to be capable of producing hypoprothrombinemia in laboratory animals. These workers studied several compounds with different side chains, but only 2-phenyl-1, 3-indandione was found to have a hypoprothrombinemic effect comparable to that of Dicumarol. In their experience compounds with 3 ketone groups were more effective in producing hypoprothrombinemia than those with 2 ketone groups. In 1947 Meunier, Mentzer and Molho,[2] during a study of chemical structures possessing activity against vitamin K, reported phenyl-

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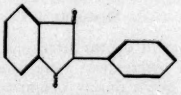
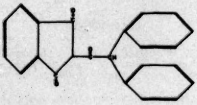
indandione or 2-phenyl-1, 3-indandione to be effective in its hypoprothrombinemic action in laboratory animals; its formula is as follows:



Further investigation of this compound was carried out in the laboratory,[3-6] and, since 1948, it has had practical application as an anticoagulant in human patients.[7-23] Recently, another indandione derivative, 2-diphenyl-acetyl-1, 3-indandione, has been put to clinical use.[24-27] Its chemical structure is as follows:



It appears to be more potent than any other anticoagulant for oral administration, perhaps because of its 3 ketone groups as suggested by Kabat et al.[1]

The exact mode of action of these noncoumarin anticoagulants is not known, but their effect is reversible by vitamin K,[16,20,27-29] and is presumably mediated through the liver. The drug is rapidly excreted by the kidneys,[6] but the end products are not known. In therapeutic doses it frequently changes the color of urine to orange red.[14,17,19,21-23] Phthalic acid, a possible degradation product of indandiones,[1] may be responsible for the color change, particularly if combined with a urine phenol. One group reports that this color is due to phenylindandione itself.[19] The orange-red color occurs in alkaline urines and can be bleached with acid to distinguish hematuria.[30]

Background

Phenylindandione was first investigated clinically in 1947. Guéguen and Soulier,[7] using single doses of 10 to 20 mg. per kilogram of body weight in 38 patients, noted increasing prothrombin times after twelve hours, therapeutic levels in most of the patients at eighteen hours and a return to nearly normal prothrombin times forty-eight hours after the initial dose.[7] They stated that there was little difference between the activity of 10 and 20 mg. per kilogram of body weight. It is believed that these investigators used a crude preparation of phenylindandione, apparently not comparable, milligram for milligram, with present preparations.[19] Using initial doses of 2 to 4 mg. per kilogram of body weight (total of 150 to 400 mg.), various authors have confirmed the characteristics of phenylindandione (therapeutic response in twenty-four to forty-eight hours, short duration of action and restoration to nearly normal prothrombin times within forty-eight hours of withdrawal of the drug), which places it as an anticoagulant between the rapid action of Tromexan and the delayed prolonged action of Dicumarol.[12,19,21] It has been praised for its uniformity of action and ease of control.[19,21] It has been said to approach the criteria set for an "ideal" anticoagulant more closely than any other agent used thus far[19] and to be the anticoagulant of choice.[14]

Clinically, a 150-mg. initial dose has been used effectively in pathologic conditions,[20] as has a 500-mg. dose.[23] Frequently little acceleration of effect has been noted when the initial dose is varied from 100 to 300 mg.[22] This wide range of action is not true of succeeding doses after a therapeutic level has been reached, when the patient becomes increasingly sensitive to small dosage increases.[6] The largest widely used initial doses have been 300 mg. followed in twelve hours by a second dose of 300 mg. and in twelve more hours by 100 mg.[19] Daily maintenance doses have been reported as being between 25 and 100,[17] 25 and 300,[19] 50 and 200[21] and 12.5 and 300 mg.[22]

Initial resistance to the drug has been reported,[17] but most observers favor the view that all patients will respond to adequate doses.[12,13,19,22] Delayed resistance in a patient initially sensitive to the drug has been reported,[17] but another group noted no altered tolerance during therapy.[13]

Most authors have expressed the opinion that divided doses give more constant therapeutic levels,[12-14,17,19,21] but this apparently increases the total daily amount as compared to the single daily dose.[12,13] The necessity of a divided-dose schedule has recently been questioned.[22] Early investigators doubted the efficacy of vitamin K (water soluble) in reversing the hypoprothrombinemia induced by phenylindandione.[1,5,6,-8,18] Considerable work, however, has demonstrated that vitamin K_1 is as effective an antagonist to phenylindandione as it is to coumarin anticoagulants.[15,17,19,20,23,28]

Soulier and Guéguen[3] noted no constant toxicity to the drug until 400 mg. per kilogram of body weight of their preparation was given to animals, when tubular damage, believed to be due to deposition of crystalline degradation products, occurred. Tubular damage by fatty degeneration has also been reported with toxic doses.[5] Transient proteinuria has been observed for several days after the beginning therapy.[19] Liver, hematologic and urinary toxicity have not been described clinically.[6] The infrequency of hemorrhagic complications in acute toxicity studies in animals and in excessive hypoprothrombinemia in human beings has provoked comment.[7,12,17,19,22,31] In addition to hemorrhage, polyuria, polydipsia and dryness of the mouth were noted by Soulier and Gueguen[3,7] in patients receiving very large doses of phenylindandione. In connection with polyuria and associated symptoms, a diuretic effect in animals receiving large doses has been reported.[11] The question whether or not various preparations are comparable has been raised[19] since

such variable responses to the drug were reported early in its use.

Method

In the evaluation of an anticoagulant the following qualifications should be analyzed: the rate of absorption and utilization as measured by the time it takes to produce hypoprothrombinemia; the rate of elimination as measured by the disappearance of hypoprothrombinemia; the consistency of dosage from patient to patient, day to day and week to week; the presence or absence of toxicity or complications; the cost of the drug as compared with that of other anticoagulants; and the route and convenience of administration. We considered these deciding factors in forming our impression of how closely phenylindandione approached the much-sought "ideal anticoagulant."

The Link–Shapiro modification of Quick's method of prothrombin determinations with whole plasma and a 12.5 per cent dilute plasma was the technic used in our study.[32] The thromboplastin was Simplastin.

We consider the 12.5 per cent plasma prothrombin time the most accurate one-stage determination since it is least affected by coexisting pathologic conditions that may interfere with the one-stage whole-plasma prothrombin determination.[33] The dilute determination was therefore the means of evaluating the hypoprothrombinemic effect of phenylindandione. The therapeutic range was considered to be two or three times the normal 12.5 per cent plasma prothrombin time of thirty-three seconds. Prothrombin times were measured daily except Sundays for the most part, although a few patients receiving anticoagulants for several months had weekly determinations.

Table 1. *Indications for Anticoagulants.*

Diagnosis	No. of Patients
Acute myocardial infarction	34
Thrombophlebitis	28
Coronary insufficiency	10
Atrial fibrillation with emboli	4
Postoperative prophylaxis	3
Raynaud's disease, with scleroderma	1
Severe peripheral vascular insufficiency	1
Total	81

Material

Seventy-two consecutive patients were given phenylindandione* alone or in conjunction with heparin during the first twenty-four hours of therapy. Nine patients were receiving Dicumarol when they were changed to phenylindandione without interruption. Of these 72 patients 34 were receiving anticoagulants for acute myocardial infarction and 28 had thrombophlebitis (Table 1).

*Kindly supplied as Hedulin by Walker Laboratories, Incorporated, Mount Vernon, New York.

Results

Seventy-two patients received the drug throughout the period of anticoagulation treatment, and their maintenance periods averaged twenty-three days, excluding the first forty-eight hours. Nine patients were transferred from Dicumarol to phenylindandione, and their maintenance period averaged one hundred and ninety-nine days. Fifty-five and six-tenths per cent of the patients were in the therapeutic range within forty-eight hours of the beginning of anticoagulant therapy, although only 6.9 per cent reached this level within the first twenty-four hours; 83.4 per cent were within the therapeutic range by the fifth day (Table 2). The initial doses varied from 150 to 400 mg., the majority receiving 300 mg. Most of the patients received 200 mg. on the second day (Table 3). Smaller initial doses were given patients with renal insufficiency that was primary or secondary to cardiac failure. In general, the second day's dose could be judged with some accuracy because, in almost all patients, a definite indication of the future response was given by the second prothrombin determination eighteen to twenty-four hours after the initial dose. As with other anticoagulants there was no definite correlation

Table 2. *Time Required for Therapeutic Effect.*

Interval before Attainment of Therapeutic Range	No. of Cases
hr.	
24	5 (6.9%)
36	15 (20.8%)
48	20-40 (27.8-55.6%)
72	8 (11.1%)
96	5 (6.9%)
120	7-60 (9.7-83.4%)
144	6 (8.3%)
168	4 (5.5%)

Table 3. *Doses of Phenylindandione.*

Total Dose	As Initial Dose	As Dose on 2d Day	As Average Maintenance Dose
mg.	*no. of cases*	*no. of cases*	*no. of cases*
400	15	1	
350	2	1	
300	30	7	1
250	5	6	6
200	18	26	9
150	2	12	15
100		14	18
75			9
50		4	16
25			7
0		1	

between the time required for the therapeutic range and the initial or two-day dosage total.

Maintenance doses varied widely, ranging from 25 to 300 mg. a day (Table 3). Some patients, though without noticeable change in their physiologic status, showed either a decreased or an increased response, necessitating a change in the previous average maintenance dose. This is fortunately infrequent but cannot be foreseen during therapy.

Nine patients, switched from maintenance on Dicumarol, were maintained for an average of one hundred and ninety-nine days (the longest was four hundred and twenty-seven days), and were in the therapeutic range approximately 69 per cent of the time. Prothrombin times were measured weekly and the patients were ambulatory; 72 patients, kept on the drug for an average of twenty-three days, were in therapeutic range 63.5 per cent of the time.

There were no signs of drug toxicity with the exception of intermittent gross hematuria in 1 patient for two days. She gave evidence of moderate renal insufficiency as indicated by a persistently elevated blood urea nitrogen and albuminuria before anticoagulation. She was maintained on phenylindandione within the therapeutic prothrombin range, including the period of gross hematuria when the drug was withheld, and the bleeding ceased the following day. Three patients, maintained on the drug for more than a year, had no evidence of toxicity during their courses.

Discussion

Our experience with initial doses agrees with that of other authors in that we found as little as 150 mg. to be therapeutic in certain pathologic states such as renal insufficiency, debility and cardiac failure. Although we could not consistently establish an adequate initial dose, it appeared that 200 mg. was proper for most patients suffering from one or more of these conditions. Weight seemed more pertinent than age and general physical status in the selection of dosage, but these variables were far less important than the estimation of renal or hepatic insufficiency, primary or secondary to cardiac decompensation. We favor 300 mg. for most patients, however, and we have not obtained better results with 400 mg. A few patients offer an initial resistance to phenylindandione therapy. This is discouraging, for if the drug is combined with heparin, it means more than four or five days of combined therapy. If phenylindandione is the sole anticoagulant there may be a period of five days or more during which the patient does not have the protection of the hypoprothrombinemic state. A few patients may require as much as 200 to 300 mg. daily as maintenance doses, demonstrating a relative resistance to the drug. These two factors (occasional slow effect and wide variability of dosage in a small number of patients) are the greatest drawbacks to the universal use of this anticoagulant.

In none of the patients treated did we encounter excessive degrees of hypoprothrombinemia. If the prothrombin time was slightly prolonged beyond the therapeutic range, a decrease of the previous day's dosage by fifty per cent produced a desirable range of hypoprothrombinemia within twenty-four hours. Complete withholding of the drug would have resulted in inadequate hypoprothrombinemia within twenty-four hours, presumably because of its rapid excretion.

We believe that all patients will respond to adequate doses, as others have stated.[12,13,19,22] Maintenance doses varied over a wide range (25 to 350 mg. a day), unlike those of Dicumarol in our experience, and were similar to those reported by Brown and MacMillan[22] (12.5 to 300 mg. a day). We cannot agree with the findings of others[13,19,21] that there is uniformity of response because patients who had previously been maintained on 50 to 100 mg. a day subsequently needed as much as 200 to 300 mg. This probably conforms to the "delayed resistance" reported.[17] Although increased doses of anticoagulants are often needed in patients whose cardiorenal status is improving with treatment, such changes in status were not apparent in most of our cases showing a need for larger doses after maintenance doses had seemed to be well established.

Divided doses were administered to 7 patients, but their maintenance was not made more effective than those given a single dose each day. We question the need or benefit of the regimen as advocated by some.[12-14,17,21] The percentage of time patients are maintained in the therapeutic range, as with other anticoagulants, depends on individual experience with the use of the drug, for the most part.

The method of evaluation in our survey is based on prolongation of the 12.5 per cent prothrombin time. Most other investigators use the whole-plasma or percentage prothrombin activity of whole plasma as their means of evaluation. We consider the latter a poor basis since, in diseases associated with thrombosis, inflammation and carcinomatosis, the whole-plasma determination is affected. In contrast the 12.5 per cent dilute plasma is affected either not at all or to a small degree by these situations. This may account for the lack of hypoprothrombinemia during the first twenty-four hours when our data are compared with those of other investigators.[23]

Heparin was used during the first twenty-four hours in 14 of the 34 cases of myocardial infarction in our series. Whether or not immediate anticoagulation was carried out with heparin depended on the physician's judgment of its necessity or possible benefits, and no set rule guarding its administration was followed.

The orange-red color of the urine, previously reported,[14,21-23] was noted in some specimens. The color may be confused with hematuria, but it is present in alkaline urine and is bleached by acidification, in our

experience and as reported by one manufacturer.[30] This is contrary to one report,[22] which states that the color disappears when the urine in which it appears is made alkaline. The drug dissolved in distilled water produces a slightly milky solution, which clears with acidification. Alkalinization causes the orange-red color, which clears again with acidification.

Although we have had no experience with 2-diphenylacetyl-1, 3-indandione (Dipaxin), this drug appears to be the most potent hypoprothrombinemic agent to be used clinically thus far.[24-27] It is interesting that its properties differ greatly from those of phenylindandione in spite of their similarity in chemical structure. Dipaxin gives a therapeutic response within forty-eight to sixty hours; its effect persists for ten to fifteen days, and it is roughly two hundred times as potent as Dicumarol.[27] The drug appears to be especially well suited for long-term maintenance control, and complications (bleeding) are few, as with phenylindandione.[27]

The indandiones as a group appear to be worthy of greater clinical trial than has been reported thus far, although their advantages over Dicumarol do not appear to be sufficient to displace that drug. More basic work on the determination of the end products of indandione administration should be investigated. The method of excretion may reveal the relative importance of renal output and liver "reserve" as variable factors in establishing maintenance control. Marked sensitivities seen in renal insufficiency suggest the former to be of great significance.

Summary and Conclusions

The chemistry and literature of a new group of anticoagulants, the indandiones, are briefly reviewed.

Experience in treating 81 patients with phenylindandione is described. The rapidity of response appears to be intermediary between those of Tromexan and Dicumarol. Duration of action and rapidity of elimination are shorter than those of Tromexan or Dicumarol.

A small number of patients are extremely resistant to initial therapy, and considerable time is lost in producing hypoprothrombinemia. The initial quantity of the drug does not appear to be related to this phenomenon.

A few patients exhibited either a decreased or an increased sensitivity to the drug after being maintained on moderate doses. The reason for this is not clear. In 1 case hematuria developed in association with well regulated phenylindandione therapy. Renal insufficiency was a complicating factor. No toxicity directly attributable to the drug was noted.

Although no occasion was present in our series, it is apparent from the literature that vitamin K_1 is as effective in indandione-produced hypoprothrombinemia as in that caused by coumarin derivatives.

This is an effective anticoagulant that is especially helpful because of rapidity of action and elimination, but the fact that it does not always have consistency of dosage makes initial and long-term maintenance difficult in some cases.

The drug is inexpensive to administer.

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CUTIS STRIP AND PATCH REPAIR OF LARGE INGUINAL HERNIAS*

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THE recurrence rate of large inguinal hernias of many years' duration remains high. The tissue in these cases is extremely poor, and the gap to be bridged is wide. In selected cases, in which a combined repair has been effected by a long strip of de-epithelized cutis supplemented with a cutis patch, the rate of recurrence has been strikingly low.

Skin was used for the repair of inguinal hernias by Hawley as early as 1889. Perhaps the first to use skin without epidermis as graft to repair hernias were Loewe (1913) and Rehn (1914). Some of the notable contributions made thereafter were by Eitner in 1920, Eitel in 1924, Peer and Paddock in 1937, Uihlein in 1939, Swenson and Harkins, Singleton and Stehouwer and Cannaday in 1943 and Mair in 1945.

My own experience dates back to 1938, when for the repair of large hernias I used skin, having first denuded the epithelium by vigorous scraping with a razor. Lately, I have been removing the epidermal layer from the donor area by means of a Thiersch graft before cutting the patch and strip. The same Thiersch graft is used to epithelize the raw donor site.

I insist on three days of preoperative skin preparation to lessen the possibility of infection. From the anterolateral aspect of the opposite thigh, after removal of the Thiersch graft, a strip of cutis, about 30 cm. long and 0.5 cm. wide, is cut. A patch of skin larger than the defect to be covered is dissected out. Both are completely denuded of any fat that might have been left on them by snipping with scissors and scraping with a knife until the typical white color of the dermis appears.

OPERATIVE TECHNIC

Large inguinal hernias are dealt with in the usual way, by high ligation of the sac, La-Roche's intra-abdominal technic occasionally being employed if necessary. Before reconstruction and repair the area is thoroughly cleared of all the areolar tissue, and the transversalis fascia is either sutured or repaired by invaginating tucks. The cutis strip is threaded to a Gallie needle, and suturing started at the pubic tubercle. The first turn of the cutis strip is passed through a perforation in the end of the strip and secured. Cooper's ligament (which is well exposed by separation of the transversalis fascia and preperitoneal fat from its anterior aspect) and the inguinal ligament below are united to the lateral border of the rectus-muscle sheath and conjoint muscle above. The use of Cooper's ligament is considered important.

The suturing and darning with the cutis strip is also performed by a modified Gallie technic. The strip is kept under elastic tension, and some of the turns are fixed by cotton stitches to the neighboring tissues. The ends of some of these cotton stitches are kept long to be used at a later stage. To avoid constriction of the spermatic cord at the internal inguinal orifices, the strip is inserted only through the upper border over the orifice, without catching the inguinal ligament below, and the suturing is then continued for a short distance laterally in the usual manner.

As far as possible the deeper, or fat denuded, surface of the strip is kept to the outer side. I believe that this raw surface unites more firmly with the deeper surface of the cutis patch that is laid over it.

The cutis patch is then laid over the repaired area. The first stitch anchors the medial end of the cutis patch to the fibrous tissue and periosteum medial to the pubic tubercle; the second stitch fixes it to the Cooper's ligament below, and the third binds it to the rectus-muscle sheath above. The lateral end of the cutis patch is partially split in its axis for a short distance to surround the spermatic cord, and a cotton stitch is tied at the medial end of this slit to prevent its slitting further. Ellis tissue forceps are applied to the lateral ends of the cutis patch, which are held pulled and elevated. At this stage the few cotton threads that were left long when the turns of the strips were fastened are rethreaded and passed through the cutis patch and tied over its superficial surface. This is considered an important step in keeping the cutis patch well in contact with its bed of strip-repaired area and thus preventing any dead space underneath the patch.

The cutis patch is then sutured along its lower border to the inguinal ligament, the upper border being anchored to the rectus-muscle sheath, conjoint tendon and internal oblique muscle. A few sutures are passed through the upper edge of the cutis patch and through the upper leaf of the external oblique muscle and tied over its superficial aspect. A few stitches close the slit in the cutis patch lateral to the spermatic cord. Finally, with a single stitch, the outer slit end of the cutis patch is fixed to the internal oblique muscle at its depth and to the external oblique muscle superficially.

Because of the very poor and stretched-out tissues in the region of the canal in long-standing large hernias, this method is less likely to give way to recurrence. The union is firm and admirably stands all occupational strains including those of laborers and farmers.

The steps of operative procedure are presented in Figures 1 to 4.

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Results

Approximately 15 per cent of the hernias operated on in this unit have been dealt with by this procedure,

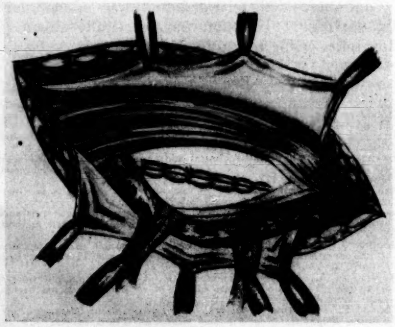

Figure 1. *First Step in Operative Procedure.*
The proximal ligated end of the hernial sac has disappeared behind the arching fibers of the internal oblique muscle, the neck of the sac having been ligated very high under traction and the sac excised. Transversalis fascia is repaired by interrupted invaginating tugs.

and many of these patients were over forty. The number of cases is not large because the procedure was only adopted in selected cases of large indirect scrotal hernias of ten to fifteen years' duration, in large direct

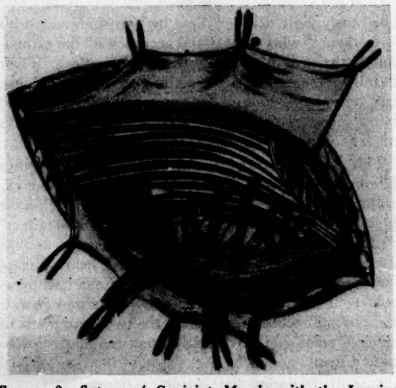

Figure 2. *Suture of Conjoint Muscle with the Inguinal Ligament by a Skin Strip.*
In large hernias the gap can only be bridged, and closure under tension is not attempted. Note the technic of closure of the internal ring.

hernias admitting three or more fingers, in other varieties of massive inguinal hernias with thinned-out tissues that have little plastic power for any safe reconstruction and in cases of recurrent hernias.

In a small series of 104 selected cases the results have been gratifying without any recurrence except in 1 case in which the repaired area slightly bulges out on coughing. This may have been due to faulty technic in not grafting the patch under sufficient tension.

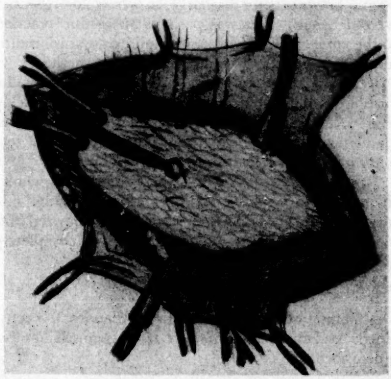

Figure 3. *Repaired Hernial Defect Covered by De-epithelized Skin Patch of Required Size.*
The patch is sutured medially to the periosteum of the pubis and rectus-muscle sheath, above to the internal oblique muscle and below to the inguinal ligament. The spermatic cord is led through a slit in the patch. Note the stitch in the patch to prevent further slitting.

This is the only case that can be considered a recurrence.

For success in this procedure great care in execution is necessary. Careful hemostasis and avoidance of

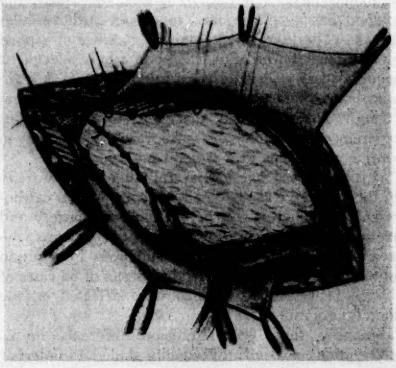

Figure 4. *Final Steps, Showing the First Stitch Closing the Slit in the Patch and Also Fixing the Spermatic Cord and Preventing It from Being Dragged Down.*
Some of the sutures pass through the leaf of the aponeurosis of the external oblique muscle and are tied superficial to it. This helps to obliterate the dead space underneath.

dead space are essential. As a routine penicillin parenterally and sulfadiazine orally (and in some

cases oxytetracycline or chlortetracycline) have eliminated the occasional redness that used to appear in the area two or three days after the operation. In some cases, in the early part of the second week, there has been a brownish oily discharge, in which no organisms were detected. This was perhaps an aseptic reaction to the cutis graft. Two cases of mild suppuration ultimately responded to vigorous antibiotic therapy.

Removal of the epidermal layer and the use of the cutis strip and patch under moderate tension quickly lead to the atrophy of what remains of sebaceous glands and hair follicles. The possibility of the formation of cysts or inclusions is thus eliminated.

I prefer skin stripped of epidermal layer to whole-thickness skin because the former provides raw surfaces on both sides and is more easily vascularized and incorporated in the surrounding tissues by completely identifying itself with the host area.

Summary

A method of repair, with cutis strip and patch combined, used in selected cases of large inguinal hernias is described.

Proper selection of cases, care in execution, prevention of dead space, absolute hemostasis and grafting of the strip and patch under adequate elastic tension are emphasized.

Grafts were well tolerated, and cysts or inclusions did not occur. Infection was practically absent in later series owing to routine chemotherapy.

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PHOTOFLUOROGRAPHIC DETECTION OF CARDIOVASCULAR DISEASE IN A GENERAL HOSPITAL*

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THE importance of the survey chest photofluorogram in the discovery of tuberculosis and other pulmonary lesions is well recognized. Recently, this method has also been used to detect cardiovascular disease. The literature contains a number of reports on the detection of heart disease in adults selected at random,[1-4] as well as in special groups such as high-school[5] and college students,[6] pregnant females[7] and others.[8] The purpose of this paper is to record our experience in detecting cardiovascular disease in routine admissions to a general hospital.

A study of this type has several inherent limitations. In the first place cardiac patients with normal cardiovascular silhouettes will be overlooked. Slattery and his associates[6,9] reviewed a group of 682 patients who received thorough medical examinations in addition to a miniature chest film. In their series of 56 cases of clinical heart disease only 25 were detected on the photofluorogram.

Secondly, there is a significant difference in interpretation, not only by equally skilled radiologists but also by the same radiologist on successive days. This was vividly demonstrated by Yerushalmy and his co-workers,[10] who studied the accuracy of the estimation of the progress of pulmonary tuberculosis. Their findings indicated that the individual roentgenologist may differ with himself 20 per cent of the time and that a given number may differ among themselves as much as 33 per cent of the time.

This does not take into consideration the further differential variation between special and regular examiners. Rutstein, Williamson and Moore[11,12] have shown in a study of 31,091 films that "special readers" (radiologists particularly interested in cardiovascular disease) detected 323 cases of verified heart disease that regular public-health chest physicians had overlooked. This source of error was minimized in our study by the inclusion, as one of the two examiners, of a senior radiologist particularly interested in cardiovascular disease.

A third limitation is the wide variation in the degree of accuracy in detecting cardiovascular disease.[13,14] This difference depends on individual criteria of abnormality. Thus, an accuracy of 100 per cent indicates that the examiner is finding only the obvious cases and overlooking a significant number of early diagnosable lesions. Conversely, detection of early disease requires a high index of suspicion, which means that many borderline cases must be followed, some of which will turn out to be normal. This per-

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Part of the expense of this study was defrayed by a grant from the New Haven Heart Association.

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spective will disclose more cardiovascular disease but will decrease the statistical accuracy of the examiner.

In the present study, no effort was made to achieve statistical perfection. The purpose was to detect as many cardiovascular lesions as possible. Consequently, all borderline cardiovascular silhouettes were included in the group for further investigation.

Finally, the frequency of abnormal cardiovascular silhouettes varies with the segment of population examined. Therefore, the older the group surveyed, the greater the prevalence of cardiovascular disease.

In spite of these limitations, the findings discovered in such a survey have proved valuable.

Technic

During 1953 photofluorograms of all adult patients admitted to the Hospital of St. Raphael were studied for cardiovascular disease. A standard 200-milliampere photofluorographic unit with a rotating anode tube, 102-cm. tube-screen distance and 70-millimeter cut film was employed. In addition to the routine posteroanterior film a left lateral view was taken on all patients except the very obese and the prenatal group. Satisfactory lateral films were obtained by means of a variable lead rubber shield, which covered the unused portion of the screen.

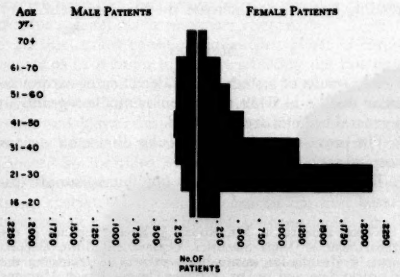

Figure 1. *Population Surveyed.*

Almost every film was initially interpreted by a third-year resident in radiology, and all films were finally examined by a senior radiologist. The patients with suspicious cardiovascular silhouettes were selected for further study, which consisted of a complete blood count, urinalysis, serologic test for syphilis and, whenever possible, an electrocardiogram and clinical evaluation by a resident in cardiology. Radiologic follow-up study consisted of a teleroentgenogram or cardiac fluoroscopic examination or both.

After complete evaluation the cases of proved disease were classified etiologically according to the criteria of the New York Heart Association.[15]

Complete follow-up studies on all patients could not be obtained because many patients were admitted for minor procedures and were discharged before a clinical cardiac evaluation could be made. Also, some patients refused to co-operate, and in a few cases the attending physician asked that the patient not be studied. We believe that the group that was not followed does not bias the results.

Findings

The population surveyed consisted of 6439 adults, 709 of whom were suspected of having a cardiovascular abnormality on the basis of the admission photofluorogram (Fig. 1 and 2). Follow-up study of 595 revealed 497 (83 per cent) to have cardiovascular disease. The causes of these cases are presented in Table 1.

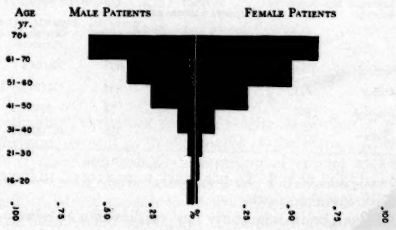

Figure 2. *Distribution of Photofluorograms Reported as Abnormal.*

Of the 595 patients followed 416 (69 per cent) were evaluated for prior knowledge of the cardiovascular disease. One hundred and ninety-six (47 per cent) were unaware of the presence of such disease, and this is consistent with the results of other studies.[1,7,10,16] Because of many biasing factors it was not deemed advisable to present a detailed breakdown of these data into the various major services (Table 2).

Table 1. *Causes of Proved Cases of Cardiovascular Disease.*

Cause	No. of Cases
Hypertension	166
Arteriosclerosis	253
Rheumatic fever	29
Congenital anomaly	6
Anemia	2
Hyperthyroidism	2
Syphilis	1
Unknown	38
Total	497

The surgical group consisted of 3305 adults, 512 (16 per cent) of whom were suspected of having an abnormal cardiovascular silhouette. Follow-up study of 437 revealed 368 (84 per cent) to have cardiovascular disease.

The relatively small medical group consisted of 477 patients; 156 (32 per cent) had abnormal photofluorograms. One hundred and thirty-four were followed, and 121 (90 per cent) of these had cardiovascular disease.

The young obstetric group consisted of 2657 women, 41 (1.5 per cent) of whom were suspected of having a cardiovascular lesion. Twenty-four were followed, and only 8 (33 per cent) were proved to have cardiovascular disease.

TABLE 2. *Summary of Data.*

Hospital Service	No. Surveyed	Suspect Photofluorograms	Follow-up Result	
			Total No. Followed	Patients with Abnormal Findings
Surgical	3305	512	437	368(84%)
Medical	477	156	134	121(90%)
Obstetric	2657	41	24	8(33%)
Totals	6439	709	595	497(83%)

Throughout this study no cardiovascular abnormalities were detected solely on the lateral photofluorogram.

Discussion

The frequency of cardiovascular disease in the population studied is much higher than that reported in the usual mass survey. This is primarily due to two factors:

The average age of these hospital patients is greater than that found in the usual mass survey. Since the prevalence of cardiovascular disease increases with age there is a relatively higher frequency in our hospital group (Fig. 2).

A significant number of patients were hospitalized because of cardiovascular disease.

The surgical group is biased by some selection, which is unavoidable since the surgeon does a certain amount of screening. For example a patient with serious cardiovascular disease is not commonly admitted for an elective surgical procedure. In spite of this fact 437 (13 per cent) of the surgical group had verified cardiovascular disease. It is unlikely that all these cases were known to the surgeons. Because the findings were called to the attention of the surgeon many of the patients benefited. In a few cases the complete cardiovascular study led to a correct diagnosis of the patient's illness.

The medical group is relatively small since the study was limited to ambulatory patients, and many patients admitted on this service were quite ill. As a result, many with known cardiac disease were not included in the study. The frequency of abnormal photofluorograms in this group is great — 156 (32 per cent) — and is probably a reflection of the older age of the medical patients.

The prenatal group deserves particular comment. It is well established that hypervolemia of pregnancy is associated with increased prominence of the pulmonary artery. This is somewhat accentuated by the 102-cm. tube-screen distance. As a result many normal cardiovascular silhouettes were called suspicious during the early days of the study. This experience, which resulted in a revision of the criteria for abnormality relatively early in the study, was the principal cause for the low degree of accuracy. The prevalence of reported abnormal photofluorograms in the prenatal patients was 41 (1.5 per cent). This is in the range that one might expect in young adults selected at random.

The value of the lateral chest view in the detection and localization of thoracic lesions is well established. In the present study no cardiovascular abnormalities were discovered solely on the lateral photofluorogram. On the other hand, this view frequently confirmed an impression derived from the posteroanterior projection. Mathisen, Morris and Wilson,[17] noted that body build, scoliosis and pectus excavatum were among the factors that increased the number of false-positive diagnoses. The lateral view was of value in appraising these factors. As a result the number of photofluorograms that might otherwise have been called abnormal was reduced. In essence, the lateral projection helped to increase the accuracy of the reading but did not increase the absolute yield.

Summary

The results of a study of the detection of cardiovascular disease in 6439 admission photofluorograms in a general hospital are presented.

The prevalence of cardiovascular disease on various hospital services is analyzed.

The value of the lateral photofluorogram is discussed.

We are indebted to Mr. Robert J. Keehn, director of the Department of Vital Statistics, Connecticut State Department of Health, for invaluable assistance in reviewing the statistical data and to Drs. William Cohen, Joseph Mignone and Lester Joseph, who helped outline the study and evaluate the clinical problems.

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MEDICAL PROGRESS

BIOCHEMISTRY OF HUMAN CANCER*

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THE medieval alchemist tried to transmute base metals to gold without essential knowledge of the laws of physics and chemistry, and hence failure was his lot, although popular fancy long sustained such efforts. With the prerequisite basic knowledge, transmutation of the elements today is commonplace, and of ever-increasing importance. The search for a cure for cancer, before an understanding of mechanisms controlling cell growth and the integration of cell populations has been achieved, bears an obvious analogy. The 5031 recorded trials of antitumor agents in lower species show the limitations of the random chemotherapeutic approach to cancer control.[1,2]

In this review consideration is first given to carcinogenesis in relation to factors affecting the function of cell proteins. The second section summarizes certain chemical properties of tumors that surpass those of non-neoplastic tissues and therefore may be related to the increased growth-potential characteristic of cancer. In the third section some of the newer concepts concerning the manner in which neoplastic tissue exerts an adverse influence on the host, apart from purely mechanical factors, are considered. Finally, some aspects of hormonal growth regulation are surveyed in relation to the treatment of certain common human tumors. This review avoids when possible duplication of the contents of numerous other excellent recent summaries and reviews,[3-6] which should be consulted on their particular subjects.

CARCINOGENESIS

The location, type and behavior of spontaneous and induced cancers vary widely from species to species. Within a single species, and particularly in man, wide individual variations occur in sensitivity to cancer induction, as well as in the course of the disease when it is once established. Inbreeding of species makes cancer more reproducible for study but obscures variability, which appears to be one of its attributes. From the biochemical standpoint the utilization of animals for cancer research has serious limitations. Florkin[7] recently summarized some of the increasing evidence for the evolutionary development of cellular biochemical systems and accompanying physiologic mechanisms. For example, primates differ from rodents in their sensitivity to carcinogenesis by estrogens and hydrocarbons,[8,9] in steroid metabolism,[10] in the composition of nucleic acids within the nucleus,[11-13] in sensitivity of cell membranes to hemolytic agents,[14] in the role of acid phosphatases in prostatic physiology,[15] in sensitivity to the lethal effects of ionizing radiation,[16] in the absence of proof for viral etiology of malignant tumors[17] and in many other ways.

Any simple explanation of the nature of the carcinogenic process is rendered more difficult by the absence of any qualitative biochemical or immunologic difference thus far identified between cancerous and noncancerous homologous tissues of man or lower species, and by the wide variety and large number of experimentally proved carcinogenic agents that have been discovered[9,18] and the carcinogenic factors implicated in human disease.[19]

However, in a number of respects the activity of carcinogens resembles agents that "denature" various types of proteins (Table 1). In some instances, such as the physical agents, denaturing activity has been proved for known human carcinogens.[20,21] The chemical process of denaturation is exemplified by the initial changes occurring in a purified protein in aqueous solution during thermal coagulation. As the temperature is elevated, the increasing kinetic energy of weaker secondary bonds leads to their rupture, producing a marked decrease in solubility. This process can be measured by the increase in free reducing groups that result in part from the conversion of disulfide (R-S-S-R) to sulfhydryl (R-S-H) groups.[45]

Initially, studies of protein denaturation used heat

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as the denaturing agent and solubility changes as evidence of the reaction. When more delicate chemical and later immunologic methods[28] were applied to the study of this process, a wide variety of physical and chemical agents were identified as inducing analogous changes in many types of human and animal proteins. detergents) and the protein undergoing denaturation.[29] The Millers have recently described the formation of a conjugation product between a metabolite of an azo-dye hepatic carcinogen (p-dimethyl-aminoazobenzene) and a liver-cell protein.[31,34,35] Similar observations have been made for a few other carcino-

TABLE 1. *Comparison of Protein Denaturation and Carcinogenesis.*

FACTORS COMPARED	PROTEIN DENATURATION	CARCINOGENESIS
A. Solubility requirements for effective agents	a) Aqueous solution required; lyophilized proteins very resistant.[20,21]	a) Hydrocarbon agents lipid soluble but act on colloidal aqueous systems b) Some carcinogens (such as urethane & alkylating agents) are water soluble[9]
B. Physical agents	a) Heat[20,21] b) Ultraviolet radiation[20,21] c) Gamma radiation & x-rays[22] d) Visible light plus photosensitizer[20,21] e) Formation of monomolecular films[20,21]	a) Ultraviolet radiation b) Gamma radiation & x-rays c) Visible light plus photosensitizer (xeroderma pigmentosum)[9,23]
C. Chemical agents (classes of compounds)	a) Detergents, including bile salts[24] b) Acids & alkali[20,21] c) Alcohol & acetone[20,21] d) Urea, guanidinium salts[20,21] e) Salicylates[20,21]	Sex steroids[25] Several hundred aromatic hydrocarbons, amines, azo-dyestuffs, & alkylating agents[9,18,26,27]
D. Inhibitory factors	a) Phospholipids (against detergents)[29] b) Added protein[29] c) Formation of sulfhydryl groups characteristic of denaturation[20,21]	a) Phospholipids (against benzpyrene, agent from coal tar)[9] b) High-protein diet[9] c) Noncarcinogenic sulfhydryl binding agents inhibit many carcinogens,[9] which may bind to thiols[30]
E. Specificity of action	Each denaturant produces more or less characteristic pattern of change in protein[20,21]	Carcinogenic action depends on host species & tissue locus of concentration[9]
F. Reversibility of action	Reversal of effect possible, within specific limits; beyond these, denaturation permanent, continuing after removal of agent.[20,21]	Hyperplasia induced by carcinogens reversible if agent is withdrawn in time; once malignancy established, presence of agent no longer necessary for growth.[21,23]
G. Effects on proteins	a) Combine with proteins[24,30,32] b) Amino acid composition & nutrient value unchanged [20,21] c) Antigenic composition altered or destroyed, depending on type & degree of denaturation[20,29]	a) Combine with proteins[21,34,35] b) No qualitative amino or nucleic acid difference known between homologous neoplasms & tissues of origin[6,36] c) Tumor proteins can serve as excellent nutritional sources[37] d) Antigenic differences reported for homologous tumor proteins[39] e) Transplantation studies indicate that cancer tissues resemble embryonic tissues in developing less marked tissue and humoral immune response in host animals than adult differentiated tissues[40,41]
	d) Denaturation destroys enzymatic function of proteins,[20,21] which may be earliest evidence of chemical alteration of protein	f) Cancer cells tend to lose specialized synthetic functions, such as 1) Iodine concentration (thyroid) 2) Acid secretion (stomach) 3) Melanin production (melanomas) 4) Proteolytic and lipolytic enzyme production (pancreas) 5) Acid phosphatase synthesis (prostate) 6) Keratin synthesis (undifferentiated epidermoid cancers)
	e) Denatured proteins more sensitive to hydrolysis by proteolytic enzymes[20,21]	g) Cancer cells apparently more susceptible than normal homologues to action of proteolytic enzymes in some cases; human gastric carcinoma lacks resistance to peptic digestion, which is property of gastric mucosa.[42]
	f) Complex proteins suffer loss of functional prosthetic groups, such as heme in hemoglobin, with resultant loss of normal function[20,21]	h) Many types of cancer manifest deficient respiration in vivo & in vitro — for example, marked decrease of iron porphyrin prosthetic groups concerned in oxygen transfers in hepatomas[43]
	g) All denaturing agents lead to cell destruction in sufficient dosage[20]	i) Some carcinogens highly lethal to cells, in adequate dosage — for example, physical agents, azo-dyes & alkylating agents[9,34,37]

Because the nature and action of these agents damaging protein structure are in many respects similar to those of carcinogenic compounds, the hypothesis appears warranted that the cellular alteration resulting from carcinogens is a manifestation of denaturation of cell proteins.

Temporary chemical bonding can sometimes be demonstrated between a denaturing agent (such as gens,[32] and binding of these substances to serum proteins has been demonstrated.[46] Nitrogen mustard compounds, which are highly reactive biologic alkylating agents, are also effective protein denaturants.[33] They were the first members of this class of carcinogens to be recognized by Haddow and his co-workers in England, who subsequently developed additional carcinogenic alkylating agents of relatively simple

chemical structure, which are believed to interfere with nucleoprotein metabolism through their "cross-linking" capacities with various types of protein.[26,27]

Denaturation of protein offers a chemically definable initial pathway of action for many of the better known physical and chemical carcinogens. As the Millers have also demonstrated, once the reparative and regenerative activities of the damaged cells have resulted in unrestrained growth, the abnormal protein-carcinogen complex may entirely disappear.[31] This suggests that the protein composition of the damaged cells has become permanently altered, which could only be established through genetic mutation. A better understanding of the biochemical basis of cancer induction will be forthcoming when methods are developed to correlate the denaturation of isolated proteins by carcinogens under controlled conditions, with their effects upon the self-reproducing proteins of the cell in the more complex biologic environment. Not only may additional cancer-inciting agents be discovered thereby but also methods may be developed for the inhibition of carcinogenesis, utilizing some of the knowledge of factors inhibiting protein denaturation (Table 1).

Tumor Composition

Nucleus

Caspersson's investigations by ultraviolet microspectrophotometry of the composition of individual human cells have provided semiquantitative evidence for the striking accumulation of nucleic acid compounds within the nucleus and cytoplasm, under favorable nutritional conditions.[47] The ultraviolet absorption spectrum of tumor cells was shown to be closely similar qualitatively to that of solutions of nucleic acids. Cells lying in the central portion of small metastases contain far less ultraviolet-absorbing material than those in the actively growing peripheral portions, which were closer to the capillaries of the host. Nucleic acids containing pentose sugars (PNA) are found both in the nucleus and in the cytoplasm of all cells, varying widely in concentration from tissue to tissue according to the local demands for protein synthesis for growth or secretion.[47] Desoxypentose-containing nucleic acids (DNA) are found only within the nucleus of diploid cells and are believed to serve as part of the structural components of chromosomes.[48] The quantity of DNA per cell is fairly constant for all diploid somatic tissues of an animal species.[47,49,50-52] Sperm and egg cell contain half the amount of DNA per cell, with considerable cytoplasmic DNA present in the egg.[48] Cells preparing to divide by mitosis synthesize increased amounts of DNA until they contain about twice the normal concentration just before cell division occurs. There are now a number of histochemical and chemical methods available for the estimation of DNA[53,54] as well as methods for the investigation of its finer structure[52] and synthesis.[48]

In spite of observed chromosomal deformities,[55] human carcinoma cells have much the same DNA concentration as that found in homologous epithelium.[48,-51,56,57] Increased DNA has been noted in some animal cancers.[58,59] Only in cases of rapidly proliferating leukemias and lymphomas have significant increments been noted in the unit-cell content of DNA.[60] In the liver, whose cells normally exhibit increased DNA concentration compared to other somatic tissues as a result perhaps of chromosomal polyploidy or polyteny, no change has been found in DNA concentration after azo-dye carcinogenesis.[61-63] In carcinomas, the rate of cellular proliferation appears often to be nearly balanced by cell death, the poorly soluble DNA being removed by phagocytosis or enzymatic depolymerization. The ratio of total DNA to potassium (as a measure of surviving cell mass) is unchanged from the normal in human tumors.[64,65]

This constancy of DNA provides a nearly ideal base line for comparison of other properties of carcinomas with normal epithelium, since it provides a measure of the active cell mass of each specimen, and has been found very useful for this purpose.[48,65] Human and animal tumors contain from 10 to 90 per cent noncancerous stroma.[66-68] The total amino acid composition of malignant tumors often reflects the high glycine and proline content of stromal connective tissue,[36] no other quantitative or qualitative differences being manifest.[69] Part of the present ignorance of the quantitative aspects of comparative cellular biochemistry of human and animal cancers stems from past neglect of the fundamental precaution of comparing *equal masses of viable normal and cancerous cells*, which is now readily possible.

In addition to sugars both types of nucleic acids contain purine and pyrimidine bases, in ratios characteristic for each animal species.[48,52] These bases and sugars are joined through phosphate linkages to form huge molecules, with molecular weights as high as 3,000,000. The intricate and probably species-specific arrangements of purines and pyrimidines are sometimes considered to be templates for the orderly reproduction of proteins or nucleic acids. In the nucleus such a process would result in the reproduction of the genetic apparatus of the cell, including new chromosomes, and in the cytoplasm in the reproduction of enzymes and structural proteins.

In human tissues there is a characteristic ratio of purine to pyrimidine bases in DNA distinct from the ratios in other species.[70] Some reports suggest that the nucleoproteins of neoplastic cells may differ in structure from those of homologous normal tissues.[59,71] However, no significant difference has been noted in the ratio of purine bases to one another in DNA of normal and neoplastic human specimens[13,70] or of pyrimidine bases.[70] Similar observations have been made for the purine-pyrimidine ratios of DNA in hamster tissues, no difference having been found in a transplanted methylcholanthrene-induced sarcoma, as

compared with normal testis, liver, spleen or kidney.[13] Better methodology, however, may in time reveal significant structural differences of cancerous nucleoproteins, such as might be expected from abnormalities of chromosomal activity during mitosis.

Because of the critical importance of nucleic acids in reproduction and growth, a highly significant area of current cancer research is concerned with the metabolism of DNA and PNA. With radioactive isotope tracers it has been possible to measure rates of incorporation of various components into the nucleic acids.[48] From these studies much information has been gained concerning the formation of purines and pyrimidines in rodents, which shows that for the most part such synthesis occurs from the simplest of molecules — such as carbon dioxide, ammonia, formate and glycine. However, an alternative route of synthesis of nucleic acids is available in some species[12]; small amounts of adenine, for example, are directly incorporated into nucleic acids.[72] The rate of adenine incorporation was the same in normal and cancerous animal tissues. When certain substituted derivatives of adenine or guanine are administered to animals, extreme toxicity occurs,[73] causing severe injury or death of tumor cells. The toxicity of purine antimetabolites may be prevented by the destruction of the compound by enzymes, as in aza-guanine in man,[74] and also appears related to the mitotic rate of tissues, which often varies as widely among normal regenerating tissues as between neoplastic and normal tissues. Useful chemotherapeutic activity has been reported for 6-mercaptopurine administered to patients with leukemia or rapidly growing lymphoma, but in patients with metastatic carcinoma, destruction of normal bone marrow may occur before the slower growing tumor tissue acquires sufficient drug to be inhibited.[75] Similar considerations probably apply to vitamin antagonists affecting nucleic acid metabolism, such as the folic acid antagonists.[76] Since there appears to be hope for some improvement in selective action of nucleic acid antimetabolites, this approach to therapy is being actively pursued at present.[77,78]

Dounce[79] has found many enzymes remaining in whole nuclei separated from cytoplasm. In general, comparable enzyme activity persisted in nuclei of tumors and in normal tissues, but some increase was noted in acid and alkaline phosphatase of neoplastic nuclei. As he has pointed out, the extraction procedure favors the loss of highly soluble enzymes such as the phosphatases. The strong binding of DNA with acid phosphatase reported by Ohlmeyer[80] may partly explain the persistence of such enzymes in extracted nuclei and may be involved in their function as pointed out below.

Cytoplasm

Cytoplasmic PNA appears from isotope incorporation studies to be synthesized at one fifth the rate of nuclear PNA,[81] without significant differences occurring in tumors except for some evidence of an increased amount in human tumors.[82] Correlation between PNA synthesis and secretory or growth activity is imperfect and has been the subject of some differences of opinion.[47,83-85]

Cell fractionation by physicochemical methods has not yet provided significant evidence of qualitative metabolic differences either in the formed elements of the cytoplasm in cancer or in the soluble protein or nonprotein fractions remaining after removal of mitochondria and microsomes.[86] Malignant tissue slices generally respire less well than normal tissues, and produce considerably more lactic acid under aerobic conditions, as pointed out by Warburg[68] in 1925. This relatively high aerobic glycolysis is present in a variety of human and animal cancers but not in non-neoplastic tissues, with few exceptions such as the retina of warm-blooded animals, and some samples of lymph nodes.[87] This finding is one of the milestones of cancer research, indicating biochemical degeneration in tumors.[88] Neoplastic rat and mouse tissues have been shown to have the necessary enzymatic content for carrying on the Krebs tricarboxylic acid cycle, through which lactic acid is normally rapidly removed after conversion to pyruvate.[89] Since cell trauma insufficient to cause death may result in increased aerobic glycolysis of non-neoplastic tissues, this trait of tumor cells has been suggested to be a manifestation of cell injury in vivo.[88] Carcinogenic azo dyes have been shown to interfere with respiratory enzyme activity such as succinic dehydrogenase.[90]

More recent investigation of cell metabolism using homogenization procedures has tended to overemphasize the respiratory insufficiency of malignant tumors. Homogenization releases enzymes that rapidly destroy pyridine nucleotides, resulting in failure to use energy obtained from tissue oxidations.[91] Tumor-tissue metabolism may be somewhat more readily affected by this procedure, since cancers appear generally deficient in pyridine nucleotides.[92] In tissue slices or homogenates properly fortified with these substances, significant differences in the intermediary metabolism of carbohydrates or fats have not been identified in tumors compared to normally regenerating tissues.[93,94] In keeping with the variability of the carcinogenic process emphasized above under carcinogenesis, a variety of somewhat different metabolic pathways may be utilized by different cancers to achieve survival and growth in different hosts.[94] However, the synthetic cell activities of all tested cancerous and noncancerous tissues fundamentally depend on the continued availability of high-energy phosphate compounds.[95,96] Thanks to the pioneering investigations of Lipmann,[97] understanding of the role of high-energy phosphate compounds has been rapidly increasing. With their use in connection with relatively simple enzyme-substrate systems, controlled studies of protein,[98] cholesterol[99] and other important biosyntheses that are now possible, may in time lead to a better understanding of the factors rendering tumor

TABLE 2. *Biochemical Properties of Cancer Cells Surpassing Normal.*

PROPERTY	TISSUE	AMOUNT OF CHANGE	REMARKS
A. Cell* constituents			
1. Desoxyribosenucleic acid (DNA) per cell	Human lymphatic leukemia lymphocytes vs. normal lymphocytes	4x often found in neoplastic cells*	2x* in circulating lymphocytes; occasional 4x* present in regenerating cells in normal lymph nodes.[89]
	Mouse leukemia vs. spleen	None	Transplanted tumor DNA increased over host tissues, in general[113]
	Mouse mammary cancer a) Spontaneous b) Transplanted Mouse prostate a) Squamous metaplasia b) Carcinoma	3x most frequent* 2x, 4x most frequent* 2x[89] 2x*	Normal breast & prostate 2x*
2. Histamine per cell	Human myeloid leukemia	250-fold ihcrease over content of myeloid leukocytes per cell	Slight increases noted in myeloid leukocytes of allergic patients, & greater increment in polycythemia vera; reduced activity in leukocytosis & leukemoid reactions; no histamine in blast cells or lymphocytes.[116-118]
B. Enzymes			
1. Beta glucuronidase	Human carcinomas	6-fold to 26-fold increment	Comparison on tissue weight basis[119-121]
	Human leukemia: a) Chronic lymphatic & myeloid b) Acute myeloid c) Acute lymphatic	Reduced[122] Up to 3-fold increase Same as normal buffy coat	
	Mouse mammary carcinoma	1½-fold to 13-fold increase	Uniform decrease noted in esterase activity of these tumors[123, 124]
	Rat hepatoma vs. liver	Reduced	Comparison on both weight & DNA basis[125]
2. Acid phosphatase	a) Human adenocarcinomas (except prostate) b) Sarcomas c) Epidermoid & undifferentiated carcinoma	Up to 2½-fold increment 2-fold increment Small increases noted in lung & skin neoplasms; reduced mean activity in esophageal cancer.	Inflammatory lesions & most benign tumors have normal or reduced activity; acid phosphatase corrected for "active cell component."[48, 126]
	Prostate carcinoma	Reduced activity present, but usually still in excess of that present in other tissues	Comparisons made on tissue weight basis[58]
	Leukocytes of polycythemia vera	46% increase	Marked decrease found in alkaline phosphatase activity (measured on per-cell basis)[118, 127]
	Chronic myelogenous leukemia	62% increase	
	Rat hepatoma vs. liver	Reduced	Ground tissues used; comparisons made on tissue weight basis.[128]
3. Incorporation of orotic acid into pyrimidines	Carcinomas of rat & man	2-fold increase in ratio of uptake uridylic cytidylic acid	Normal ratio 4:1[129]
4. Amino acid incorporation	Rat hepatoma a) In vitro	Nearly 3-fold increase in rate over regenerating liver[130]	
	b) In vivo	Unchanged[130]	
	Lymphosarcoma	Unchanged[104]	
	Ehrlich ascites carcinoma	Marked increase	Compared to liver & muscle[101, 130]
5. Formate incorporation	Mouse leukemia	More rapid than normal lymphocyte	Cells immobilized in cellophane bag intraperitoneally in host[131]
6. Testosterone metabolizing enzymes	Human mammary carcinoma	In excess of that present in any other human tissue; up to 300-fold of that in liver.	Comparisons made on per-cell basis using DNA[132]
C. Vitamins			
1. Inositol	Human carcinoma	38% increase	Thiamin, riboflavin, nicotinic acid & pyridoxin decreased 21-71% of normal in these tumors[97]
2. *Strep. lactis* R factor, ("folic acid") titred against liver fraction "B" standard	Human carcinoma	2-fold increase	Rat cancers failed to show increase in inositol or "folic acid" over concentration present in normal tissue[97]
3. Folic acid	Leukemia cells vs. human leukocytes	Increased in leukemic cells	The more immature leukemic the leukocytes, the higher their folic acid content[133]

*x=DNA content of spermatid.

cells superior to non-neoplastic host cells in the competitive struggle for utilization of the common body pool of oxygen, glucose, amino acids and essential cofactors.

Under optimum conditions in vitro, tumor cells of lower species can concentrate amino acids from their environment at a high rate, exceeding the capacity of regenerating normal tissues.[100-102] In spite of this, excessive rates of amino acid incorporation have not yet been demonstrated in solid tumors in vivo.[103,104] This may again reflect the inadequate capillary blood supply of tumors that Caspersson noted to have such a profound effect on the morphology and nucleic acid content of human tumor cells, depending on their location at the periphery or in the central avascular part of metastases. Mouse tumors, for instance, contain less blood per unit of weight than normal liver, spleen or kidney.[105] Venous blood from human tumors has a higher oxygen content than that from uninvolved areas, suggesting either arteriovenous shunting or reduced oxygen extraction by neoplastic tissue.[106] Also suggesting the importance of circulatory factors in limiting the metabolism of solid tumors in vivo are the observations of the supernormal amino acid concentrating activities of Ehrlich ascites tumor cells.[101]

Inorganic constituents required for cell growth such as phosphate and potassium are taken up by tumor cells at rates little different from rapidly metabolizing normal tissues.[107] Because adipose tissues have very sluggish rates of exchange with isotopes of these or other substances, localization of tumors of the breast and an estimate of their malignancy has been possible.[108] Alterations of the blood-brain barrier adjacent to central-nervous-system cancers[109] augment the exchange of isotopically labeled dyestuffs and phosphate, so that localization is possible by means of suitable detecting devices during surgery.[110] Differentials in the rates of metabolic activity of neoplastic and non-neoplastic tissues, such as radioiodine uptake in some thyroid cancers, may also alter the rate of incorporation of isotopically labeled compounds, to aid in mapping the distribution of metastases or in therapy.[111-113] As a rule there is sufficient overlap in the metabolic activity of the two types of tissue to prevent consistent diagnostic or therapeutic use.[114] Even if malignant tumor cells had strikingly elevated rates of isotope incorporation under optimal conditions, the circulatory insufficiency of metastases of solid tumors and consequent necrosis would do much to reduce the rates of isotope incorporation observed in vivo.

Table 2 summarizes a few quantitative differences that have been established for tumors of human origin and may have ultimate significance in explaining the superior competitive growth properties of malignant tumors. Some discussion appears necessary particularly of three enzymes present in excessive amounts in human neoplastic tissues, as well as in the circumambient fluid of some experimental neoplasms.[134]

(To be continued)

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MEDICAL INTELLIGENCE

HEMORRHAGE FROM A BENIGN ULCER OF THE SIGMOID COLON*

Report of a Case

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WHITE RIVER JUNCTION, VERMONT

A SOLITARY benign ulcer occurring in the large intestine with no apparent etiologic source was first described by Cruveilhier[1] in 1830. Since then 83 cases of this type have been reported.[2-9] Such a lesion has frequently been referred to as a "simple ulcer" of the colon.

Of these 83 cases at least 53 were diagnosed after the ulcer had perforated. The majority of those that perforated had a fatal outcome. In many of the 30 cases that did not perforate the diagnosis was made at autopsy. Sixty-two of the ulcers were located in the cecum or ascending colon. Of the remaining 21, 11 were in the sigmoid colon. All these 11 perforated before diagnosis, and 9 of the patients died as a consequence of the perforation.

Attempts have been made to ascribe these ulcers to local neurogenic or vascular disturbances, intestinal stasis and alteration in the pH of the colon.

The occurrence of hemorrhage in this condition had not been described until recently, when profuse rectal bleeding from a simple ulcer of the transverse colon was reported by Wright.[7] In the case that he presented the lesion was demonstrated preoperatively with a barium-enema examination, but was thought to be a malignant growth.

Three other benign ulcers of the colon have been reported recently. One was found incidentally in the transverse colon[8] during gastric surgery, and exploration for acute abdominal pain showed the others to be perforating the cecum.[9] Preoperative diagnosis of simple ulcer of the colon has not been recorded, although Harrison[5] reports a case in which on barium-enema examination such a lesion was demonstrated but was thought to be an inflammatory change due to tuberculosis. The true nature of the ulcer was disclosed at operation.

In recent years experienced clinicians have tended to ascribe rectal bleeding of an undisclosed origin to diverticulosis, even though in some cases diverticula are not demonstrated by x-ray examination. The source of such bleeding may be a primary ulcer of the colon.

The case presented below is of unusual interest because hemorrhage was the chief manifestation and a preoperative diagnosis of the lesion was made on barium-enema examination.

CASE REPORT

W.G.M., a 58-year-old storekeeper, was admitted to the hospital on July 21, 1953, with the complaint of a passage of bright-red blood by rectum. Since 1950 he had had frequent episodes, lasting several days each, of soft black stools that spontaneously subsided. In April, 1953, the stools had subsequently become firm and irregular in occurrence and frequently streaked with bright-red blood. During the week before admission he had had a cramping pain in the lower abdomen accompanied by a sensation of "bloating" and increased passage of flatus. On July 18 he passed an estimated pint of blood by rectum, followed by 4 bloody bowel movements during the next 12 hours. During this time he was weak and faint, but did not lose consciousness.

Physical examination showed a pale, weak, lethargic man who appeared older than his stated age. He was well nour-

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ished, but had poor muscle tone and was moderately obese. Examination was otherwise not remarkable, except for extensive superficial varicosities of both legs.

Examination of the blood revealed a red-cell count of 3,800,000, with a hemoglobin of 11.5 gm. per 100 cc., and a white-cell count of 9000; the hematocrit was 35.6 per cent. Blood-volume studies by the Evans-blue method indicated a whole-blood deficiency of approximately 1000 cc.

After admission there was no further bleeding. The blood volume was restored to normal by transfusion of 1000 cc. of whole blood. Gastrointestinal series and barium-enema examination were interpreted as normal. Sigmoidoscopic examination to 25 cm. was negative, except for distended internal hemorrhoids. On August 14 a hemorrhoidectomy was performed. On the 5th postoperative day, tenderness, redness and swelling of the left leg developed, with enlarged, tender inguinal lymph nodes. Phlebothrombosis was suspected, and anticoagulant therapy (heparin and Dicumarol) was begun. Forty-eight hours later profuse rectal bleeding began, necessitating cessation of anticoagulant therapy and transfusion with 2500 cc. of whole blood. Sigmoidoscopic examination to 25 cm. was again negative, except that blood was visualized coming from above the sigmoidoscope. Repeat barium-enema study revealed an irregularity on the medial surface of the sigmoid colon, approximately 30 to 35 cm. proximal to the internal sphincter. This was demonstrated again on August 27. A smaller, similar defect had also been

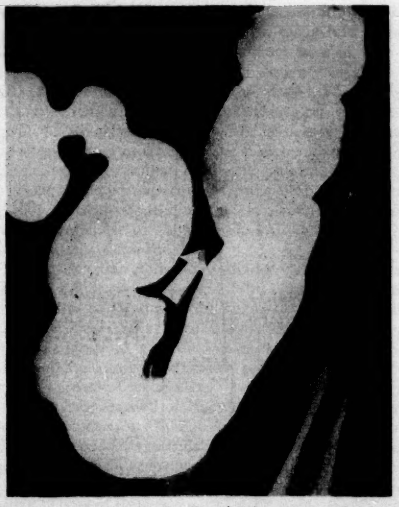

FIGURE 1. *Barium-Enema Examination (Arrow Points to the Lesion in the Sigmoid Colon).*

present at the same location on the examination of July 23; although the examinations of July 31 and July 23 had previously been reported negative it was concluded that this small irregularity of protruding barium shadow represented a lesion in the sigmoid, apparently an ulceration in this portion of the colon. The possibility of carcinoma was also considered, but in the absence of a filling defect in the lumen of the bowel, an inflammatory ulceration was regarded as more probable (Fig. 1).

On September 2 an exploratory laparotomy was performed. There were no abnormalities in the abdomen except for a freely movable, indurated lesion in the sigmoid colon at the level of the pelvic brim. This area of the colon was resected, and an end-to-end anastomosis performed.

Examination of the specimen by the pathologist revealed an ulcer, 1.0 cm. in diameter, on the mesenteric side of the colon. The mucosa and muscularis were ulcerated. A firm, white, fibrous strand of tissue, covered with a layer of granulation tissue, extended from the ulcer through the bowel wall. This suggested that the ulcer had penetrated deeper and healed. Microscopical examination did not show any signs of malignant degeneration (Fig. 2). There were no adjacent diverticula.

The patient had an uneventful convalescence and had had no further melena or intestinal symptoms 8 months later.

SUMMARY AND CONCLUSIONS

A case of benign simple ulcer of the sigmoid colon is presented. This case is unique because the chief preoperative manifestation was colonic bleeding, to our knowledge this is the first such case in which a preoperative diagnosis was made, the ulcer was demonstrated on barium-enema x-ray examination and all other reported cases of sigmoid ulcer have perforated before diagnosis.

This type of lesion should be considered in the differential diagnosis of colonic bleeding. The poor outcome in the reported cases makes x-ray diagnosis and operative treatment highly desirable.

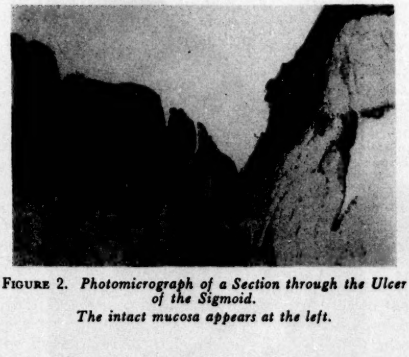

FIGURE 2. *Photomicrograph of a Section through the Ulcer of the Sigmoid.*
The intact mucosa appears at the left.

We are indebted to Drs. Norman Loud and John McCutcheon for the x-ray examinations and interpretations and to Dr. Reginald House for the tissue examinations.

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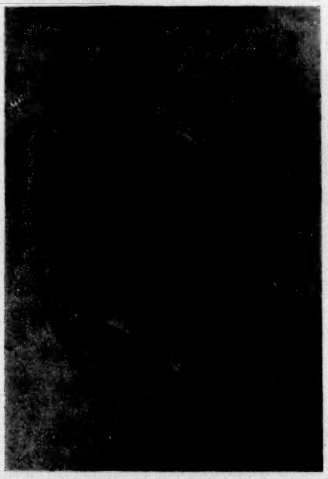
DOCTORS AFIELD

Thomas Hodgkin

HYMAN MORRISON, M.D.*

BOSTON

DURING a visit to Israel in 1950, a pilgrimage to the grave of Thomas Hodgkin in Jaffa, now adjoining the new city of Tel Aviv, left a memorable impression. Hodgkin died there on April 4, 1866, of "dysentery," in his sixty-eighth year, while accompanying his friend, Sir Moses Montefiore, on one of the many philanthropic journeys they had taken together. Sir Moses had erected, soon afterward, a monument over the grave.



Thomas Hodgkin (Reproduced from A Journey to Morocco. *183 pp. London: T. Cautley Newby, 1866).*

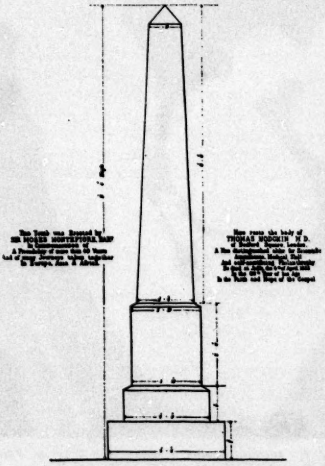
In 1927 the late Dr. Emanuel Libman, of New York, while visiting Palestine in connection with his interest in the Hebrew University in Jerusalem, located, after much inquiry, the forgotten, neglected grave. Great interest was aroused by this finding, and at a ceremony arranged by Libman he placed a wreath on the grave and said in part, "I deposit this wreath in the name of the medical profession, not simply as physicians but as citizens of the world for the benefit of whom Thomas Hodgkin strove and died."

Drs. Kriger and Sherman, eminent Tel Aviv physicians, learned the location of the Hodgkin tomb for us, through Dr. Zaki Sfeir, Arab surgeon in charge of the French Hospital in Jaffa. It was he who led us to it in the small Protestant cemetery across the way, hidden behind an abandoned English mission house. On the granite obelisk, fenced by an iron railing, there was the following inscription:

> Here rests the body of Thomas Hodgkin, M.D. of Bedford Square, London, a man distinguished alike for scientific attainments, medical skill and self-sacrificing philanthropy. Died at Jaffa on the 4th of April 1866, in the 68th year of his age in the faith and hope of the Gospel. "Humani nihil a se alienum putabit!"
>
> The epitaph is inscribed by his deeply sorrowing widow & brother to record their irreparable loss.

On the obverse is the following: "This tomb is erected by Sir Moses Montefiore, Bart., in commemoration of a friendship of more than 40 years & of many journeys taken together in Europe, Asia & Africa."

The account of this visit to the grave again raised much interest. In the following year, at the meeting of the Israel Society of the History of Medicine, a paper on Thomas Hodgkin was presented, and all those attending paid tribute to him by visiting his grave. A similar honor was extended to his memory in 1952 during the second World Congress of Jewish Physicians and again in 1953, when the seventh International Congress of the History of Science convened in Jerusalem.



Obelisk of Polished Aberdeen Granite (Reproduced from A Journey to Morocco. *183 pp. London: T. Cautley Newby, 1866).*

Thomas Hodgkin (1798-1866) was born in London, of Quaker parentage, and was educated at home and on the Continent. He began his medical training at Guy's Hospital, and after a year's study in Paris under the inspiring influence of Laënnec, he received his doctorate in Edinburgh in 1823. The introduc-

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tion of the stethoscope in England was in large measure due to him, and also the acceptance of Laënnec's emphasis on the correlation of clinical with pathological study of disease. He received the licentiateship of the Royal College of Physicians in 1825, and in the same year he was appointed to Guy's Hospital as curator of the newly established Museum and as lecturer in morbid anatomy, offered as a regular course for the first time in England.

He held these posts with distinction and outstanding achievement till 1837. It was during these twelve years at Guy's Hospital that he did all the scientific work that made him eminent and won for him recognition and membership in the scientific societies at home and abroad including those in Philadelphia and Boston.

Hodgkin is best remembered through his work, "On Some Morbid Appearances of the Absorbent Glands and Spleen,"[1] published in 1832. He had early become interested in the physiology and pathology of the lymphatic system and had collected a group of 6 cases in which the lymphatic glands and the spleen were the seat of disease. He stressed that "the enlargement of the glands appeared to be primary, rather than the result of irritation propagated from some inflamed texture, and to be the consequence of a general increase of every part of the gland rather than of a new structure; furthermore, the spleen also was involved, thickly pervaded with bodies of various sizes, resembling in structure the diseased glands. . . ." He made brief comment on the symptoms in his cases, mentioning only progressive enlargement of the lymph glands and spleen, leading to anemia, cachexia and finally death. He did not claim priority and made no further study of the condition.

Hodgkin's description lay hidden in an obscure journal[1] till Richard Bright[2] (1789-1858) recognized in it a disease of malignant character unknown till then. In 1856 Samuel Wilks, a successor of Hodgkin at Guy's Hospital, described independently "Enlargement of the Lymphatic Glands combined with a Peculiar Disease of the Spleen."[3] After he had written his paper, he learned of Hodgkin's description of the same condition in 1832, through Bright's citation. However, Wilks' comment as well as Bright's gained no more general recognition than Hodgkin's original paper until Wilks wrote a second article in 1865 entitled "Cases of Enlargement of the Lymphatic Glands and Spleen, (or, Hodgkin's Disease)."[4] This time, referring to his previous paper, he said with extraordinary generosity: "Although my own observations were at the time [1856] original, I had been forestalled by Dr. Hodgkin who was the first, as far as I am aware, to call attention to this peculiar form of disease."

Another contribution involving priority for Hodgkin was his work on aortic insufficiency, again called to the attention of the medical profession by Samuel Wilks. Hodgkin first read his paper, "On Retroversion of the Valves of the Aorta," in 1827, five years before Corrigan's celebrated presentation on the same subject. He credits a friend with having pointed out to him this valvular deformity. He, himself, had not previously met with such a lesion, nor had the French masters made allusion to it. "I shall designate by the term retroversion of the valves that disease state which allows their dropping in towards the ventricle instead of effectively closing the vessel against a reflux of blood." He described 9 specimens of this deformity of the aortic valve and cited the symptoms and physical signs in the cases he had followed. He emphasized particularly the prolonged perverted sound, detected by auscultation, comparable to "the stroke of a saw or the puff of bellows."

Still another of his observations of priority interest is recorded in his major work on pathology *Lectures on the Morbid Anatomy of the Serous and Mucous Membranes*:

> The partial inflammation of the peritoneum, in the iliac fossa, is sometimes set up by disease in the appendix caeci. If this be inconsiderable, it may merely give rise to some very limited partial adhesions; at other times, the appendix having been perforated by ulcerations, occasioned by the lodgement of faecal concretions in its cavity, extravasation takes place and inflammation of a more severe and serious kind is originated. Even in these cases, nature sometimes succeeds in limiting the inflammation to a part of the right side; but it is at other times diffused through the whole abdomen, is accompanied by symptoms of a most serious nature, and quickly proves fatal.

This Hodgkin noted more than sixty years before Reginald Heber Fitz presented his classic contribution "Perforating Inflammation of the Vermiform Appendix" in 1886.

Hodgkin resigned his post at Guy's Hospital in 1837, when he was refused the appointment to the position of assistant physician, then available, which he desired greatly in his ambition to help advance medicine to a high scientific level. This failure gave rise to much indignation among his students and friends, who regarded him as likely to become one of the great physicians of his time. They charged the treasurer at Guy's Hospital, who had the power of appointment, with having rejected Hodgkin because of his Quaker manner of living and his liberal activities.

His disappointment turned Hodgkin more and more to interests developed early through his natural bent of mind. He now devoted himself increasingly to the alleviation of the poor, to improve their housing and to provide them with adequate medical care. His early writings show interest in public health much in advance of his time. In a public lecture on the means of promoting and preserving health, delivered in 1830, he stressed the harm arising from filth, overcrowding, bad sanitation, poor housing, drunkenness, bad food, want of vaccination, lack of fresh air and exercise. In 1832, with the appearance of cholera in London, he urged the clearing and cleansing of the filthy slums, commenting on the awful poverty of its starved inhabitants and recommending as a means of alleviating unemployment the

building of new roads. He advocated reform in medical education and practice, again in advance of his time.

Through his activities in the Ethnological, the Geographical and the Aborigines Protection societies, he was concerned with the fate of primitive and oppressed people everywhere — Indians in America, Negroes in Africa and Jews in many lands. It was this interest that brought him early in contact with Moses Montefiore.

Moses Montefiore (1784-1885) was the outstanding Jewish philanthropist of his time. Born in Italy of English Jewish parentage, he was brought up in London where, after considerable hardship and even adversity, he became very wealthy and highly influential in financial, political and civic life. Queen Victoria knighted him and made him a baronet. Under all conditions and everywhere, he lived steadfastly the life of the pious, rigidly observant Jew, and devoted himself to an extraordinary degree to the alleviation of Jewish suffering throughout the world.

The friendship of these two unusual personalities was primarily based on their passionate devotion to philanthropy. Very probably they were also drawn to one another by their independence of spirit, each distinctly peculiar in his own environment, the one a rigidly observant orthodox Jew and the other a steadfast Quaker. Each had won eminence in his own field, but both are remembered more for their long friendship devoted to the betterment of human welfare.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 40481

Presentation of Case

A sixty-seven-year-old woman entered the hospital because of nausea.

The patient had been in good health until thirteen years previously, when a doctor told her that she had hypertension (maximum blood pressure of 240 systolic). She had no cardiac symptoms at that time. She was started on digitalis, which produced so much nausea and vomiting that she stopped taking it. Twelve years before admission she had a sudden attack of squeezing pain in the left side of the chest that lasted for one day and was not relieved by rest. She was placed on bed rest for three or four months. Later, an electrocardiogram showed an old "coronary." She had since had attacks of vague squeezing discomfort over the precordium largely brought on by emotional disturbances. For many years she had had attacks of "biliousness." Two months before admission she noted the onset of itching and swelling of the hands, ankle swelling, anorexia and aching in the arms and legs. She was seen in the Out Patient Department, two weeks before admission, complaining of these symptoms and in addition of facial flushing and nervousness to the extent that she required phenobarbital to sleep. Physical examination at that time revealed a blood pressure of 200 systolic, 110 diastolic, a presystolic gallop, a Grade 2 systolic murmur at the left sternal border and a pulmonic second sound louder than the aortic. The liver edge was palpated 3 fingerbreadths below the right costal margin, and she had +++ pitting pretibial edema to the knees. She was given an intramuscular injection of Mercuhydrin and started on digitalis, which she stopped after four days because of severe nausea and vomiting. With the nausea, she noted the onset of right-upper-quadrant discomfort, which sometimes radiated to the back.

Twenty-four years before admission the left breast had been removed because of carcinoma. She had injured her left eye during childhood, so that she could only see hand movements with it. Four years before admission she had an attack of acute glaucoma in the other eye, for which an iridencleisis was done. A year later a cataract extraction was performed on the right eye. She was seen in the Out Patient Department a year and a half before admission because of nervousness, a feeling of impending death, tightness in the chest, tingling in the left leg, and facial flushing. At that time the blood pressure was 180 systolic, 120 diastolic, and there was a Grade 2 apical systolic murmur with a presystolic gallop. No objective therapy was given. She was

seen in the Thyroid Clinic and dismissed as not being a thyroid problem. A psychiatric interviewer concluded that she had a "chronic anxiety state."

Her mother had died of heart and kidney disease at sixty-three, a brother had died of a cardiovascular accident at sixty-three, and another brother, with whom she lived, had had a cardiovascular accident five years previously.

Physical examination revealed a woman in no acute distress. Several observers thought that she was more darkly pigmented than normal, and the patient thought the increased pigmentation had developed during the past two months. The lungs were clear. The left border of the heart was 11 cm. lateral to the midsternal line. The cardiac findings were as before. The liver edge was palpated 7 finger-breadths below the right costal margin and was tender. There was ++ pitting pretibial edema to the midcalf.

The temperature was 100°F., the pulse 92, and the respirations 20. The blood pressure was 210 systolic, 112 diastolic.

Urinalysis demonstrated a specific gravity of 1.015, a ++ test for albumin and 2 to 5 white cells per high-power field in the sediment. Examination of the blood showed a hemoglobin of 13.5 gm. per 100 cc. and a white-cell count of 8600, with 80 per cent neutrophils. The nonprotein nitrogen was 30 mg., the fasting blood sugar 103 mg., the postprandial sugar 208 mg., the total bilirubin 1.4 mg., and the alkaline phosphatase 1.8 units per 100 cc.; the potassium was 3.6 milliequiv. per liter. The serum iron was 100 microgm. per 100 cc. (normal, 125 to 200 microgm.), and the iron-binding capacity 33 per cent. The uptake of radioactive iodine was 34.1 per cent. A stool guaiac test was negative. An x-ray film of the chest disclosed cardiac enlargement (cardiothoracic ratio of 16.5:25.5) and pulmonary congestion. An electrocardiogram showed hypertrophy of the left ventricle.

Therapy was symptomatic during further investigative studies. A Graham–Cole test done two days after admission revealed a well functioning gall bladder without evidence of stones. Liver-function studies at that time showed a total bilirubin of 2.4 mg. per 100 cc., a cephalin flocculation of ++ in forty-eight hours, a total protein of 7.1 gm. per 100 cc., an albumin of 4.0 gm., a globulin of 3.1 gm. and a cholesterol of 460 mg. per 100 cc. and a bromsulfalein retention of 44 per cent. Three days after admission she vomited 200 cc. of ++ guaiac-positive material, but a stool guaiac test was negative on the sixth and again on the eighth hospital day. Liver-function studies repeated four days after admission disclosed a cephalin flocculation of +++ in twenty-four and forty-eight hours, a prothrombin time of 100 per cent and a thymol turbidity of 4.5 units, a cholesterol of 289 mg., cholesterol esters of 189 mg. and a choline esterase of 0.55 units per 100 cc. Seven days after admission a gastric aspiration revealed no free acid and none after histamine; the serum amylase was 26 Russell units, and the alkaline phosphatase was 2.7 units per 100 cc. A gastrointestinal series eight days after admission demonstrated a small hiatus hernia and a smooth pressure defect in the proximal portion of the descending limb of the duodenum. Nine days after admission a liver biopsy showed fatty vacuolization. The bromsulfalein retention was 37 per cent, and the hemoglobin 10.0 gm. per 100 cc. Fourteen days after admission, the white-cell count was 13,500, the red-cell count 2,770,000, and the hemoglobin 10.3 gm. per 100 cc. The Wintrobe indexes were as follows: mean corpuscular volume, 112 cubic microns (normal, 80 to 94 cubic microns); mean corpuscular hemoglobin, 37 micromicrogm. (normal, 27 to 32 micromicrogm.); and mean corpuscular hemoglobin concentration 33 per cent (normal, 33 to 38 per cent). A stool was +++ guaiac positive, brown and semisolid. The direct bilirubin on this date was 0.5 mg., and the total 0.8 mg. per 100 cc. On the sixteenth hospital day a sternal-marrow biopsy showed erythroid hyperplasia.

Fifteen days after admission the patient vomited 200 cc. of coffee-grounds material containing blood clots. The blood pressure was 180 systolic, 110 diastolic, having gradually fallen from 210 systolic, 100 diastolic, on the fifth to 146 systolic, 90 diastolic, on the thirteenth hospital day. On the eighteenth hospital day a surgical consultant suggested exploration. Because of the low hemoglobin, whole-blood transfusions were started, and when she arrived on the Surgical Service at 8:00 p.m. on the sixteenth hospital day the first 500 cc. of blood was running; it was completed in sixty minutes, and the second 500 cc. started. Shortly after this she became cold, sweaty and hyperpneic. The lungs were filled with coarse, bubbling rales. She was given oxygen, Demerol and Mercuhydrin and digitalized. By 2:00 a.m. the next day the neck veins were flat, respirations were 30 per minute and regular, and there were a few fine apical rales. The heart sounds were clear, strong and regular. Later that day the blood pressure was recorded at 210 systolic, 120 diastolic, and a few moist rales were still heard halfway up both sides of the chest. Peculiar twitching movements were noted, but the Chvostek test was negative. The blood sodium was 125 milliequiv., the chloride 88 milliequiv., and the potassium 7.9 milliequiv. per liter. The serum pH was 7.45; the nonprotein nitrogen was 210 mg., the amylase 21 Russell units, and the hemoglobin 11.5 gm. per 100 cc., and the hematocrit was 35 per cent. During the preceding twenty-four hours the urinary output was 395 cc. The patient was disoriented but responsive to questioning. Spontaneous jerking movements of all parts of the body persisted. The temperature had risen to 101°F., where it stayed. Coarse inspiratory rales up to the scapulas posteriorly were still present. The cardiac findings were as before. An electrocardio-

gram showed first-degree atrioventricular block and left-bundle-branch block, which had developed since the previous tracing. Two days after this episode of pulmonary edema she was still disoriented and had become incoherent and rambling. The twenty-four-hour output of urine had fallen to 270 cc. Fluids administered intravenously in each twenty-four hours consisted of 1000 cc. in addition to the amount of the previous day's output of urine. The serum nonprotein nitrogen was 235 mg. per 100 cc., and the sodium 128 milliequiv., the potassium 7.2 milliequiv., the chloride 92 milliequiv., and the carbon dioxide 19 milliequiv. per liter. By the next day the output of urine had fallen to practically zero, and diffuse cutaneous edema was noted. On the twentieth hospital day she died quietly.

Differential Diagnosis

Dr. Edward M. McGirr*: This elderly patient had hypertension and presumably coronary atherosclerosis. She had had a myocardial infarction twelve years before admission and probably residual angina. Her present admission was occasioned by the development of the features of congestive cardiac failure, which failed to respond to treatment.

I think we can ignore the previous story of breast cancer. I have no explanation to offer for the itching of the hands or the tingling in the left leg unless, with the aching in the limbs, they were due to circulatory insufficiency eventually aggravated by the edema. There is no evidence from the data available of abnormal reflexes or hyperesthesia to indicate peripheral neuritis, and there is no mention whether the peripheral pulses were normal or abnormal. I have considered whether it is possible to offer any explanation of the flushing and nervousness. Obviously, she was too old for menopausal symptoms. The question of thyroid overactivity had been explored and ruled out. Bouts of increased nervousness in a patient with hypertension raise the question of the presence of a pheochromocytoma, but these would have been accompanied by pallor, not flushing, and there is nothing else in the history to make one think of pheochromocytoma. Indeed, the nervousness and flushing may have been part of her mental and physical make-up, the nervousness increasing with worry as her condition deteriorated.

The strong family history of cardiovascular degenerative disease suggests that the hypertension was in fact essential hypertension. In a patient with cardiac failure I should have expected a higher urinary specific gravity than 1.015, particularly if it was a morning specimen, and I think this indicates some degree of impairment of concentration so that the albuminuria was probably evidence not merely of congestion due to heart failure but also of some degree of nephrosclerosis. The 2 to 5 white cells per high-power field in the sediment I do not believe were significant. No organisms were mentioned. Though it would have been interesting to know whether any cells were found in a specimen obtained by catheterization or whether any organisms were cultured, there was really nothing to suggest pyelonephritis.

This patient with hypertension and congestive cardiac failure for some reason began vomiting blood. Such bleeding, if she had had a typical dyspeptic history, would have made me think of peptic ulceration; the histamine-fast achlorhydria is much against ulcer, as is the negative barium series, but it does not exclude a gastric ulcer, and so I have to keep this question of ulcer, the most common form of bleeding, in mind. Perhaps an incidental condition such as a gastric neoplasm developed. That would account for the recent dyspeptic symptoms, but not for the "biliousness" that she had had for many years. We do not have enough information about the "biliousness." Perhaps it was associated with headache and eye disturbances and was due to migraine. Of course chronic gastritis, ulcer, chronic cholecystitis or toxemia with kidney lesions may have produced those dyspeptic symptoms. Gall-bladder disease appears excluded by the gall-bladder x-ray series. Gastric neoplasm, though not revealed by barium-meal examination, could be an incidental condition to explain the bleeding, especially if accompanied by glandular enlargement, which might be invoked to explain the defect in the duodenum noted in the x-ray films. Incidental reticulosis, with infiltration of the stomach wall and with glandular enlargement, deserves mention at least as a possible but unlikely cause of the bleeding. The presence of the hiatus hernia makes me wonder if the cardiac sphincter may not have been incompetent, allowing the stomach contents to regurgitate, with resultant esophagitis and ulceration, but in the presence of a histamine-fast achlorhydria I am inclined to discard this as of no importance. Indeed, the opinion I favor is that these small upper gastrointestinal hemorrhages may be explained purely on the basis of engorgement of the stomach in a patient with congestive cardiac failure, perhaps aggravated by the presence of cardiac cirrhosis of the liver.

The patient had an engorged, greatly enlarged liver on admission, and I suppose the most likely explanation of the right-upper-quadrant pain that radiated to the back was the liver engorgement and stretching of the liver capsule. The liver-function tests gave evidence of impaired function. The liver biopsy showed fatty change, and there is no mention of increased fibrosis, but I should not like to exclude cardiac cirrhosis on the basis of the biopsy. Pigmentation is a common occurrence in cirrhosis of the liver. I do not know whether pigmentation is worth while considering in this patient, for there is some question about its presence, but if she had become pigmented I might wonder if the pigmentation was due to the development of cardiac cirrhosis.

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This patient had postprandial hyperglycemia; in the presence of the normal fasting blood sugar I think the postprandial hyperglycemia was a consequence of the impaired liver function, which in turn was due to the heart failure. The question of pigmentation and hyperglycemia in a patient with an enlarged liver must make me pause to mention hemochromatosis but, in the absence of supporting evidence, only to dismiss it. The dyspeptic history and the hyperglycemia make me wonder about disease of the pancreas, and the x-ray appearance of the duodenum makes me consider intrinsic diseases of the pancreas like cancer, chronic pancreatitis and cyst, but they would not explain the gastric bleeding and, I think, can be ruled out.

There is nothing in the history or findings to indicate a duodenal ulcer. Indeed, in any duodenal lesion that bled slowly the bleeding would have gone down the alimentary tract rather than up, and I think I shall also rule out any duodenal conditions like a papilloma or cancer of the ampulla of Vater. The bleeding does not suggest them. There was apparently no x-ray evidence of esophageal varices. As a final source of bleeding we might consider an aneurysm that was slowly leaking into the alimentary canal. I should want to know from the radiologist that there were no appearances suggestive of this, but I do not know where such an aneurysm would be to indent the duodenum, if this is important, and since I can see no evidence to support it, I shall dismiss it from my clinical appraisal.

The hematology in this case has worried me. The peripheral blood findings were normal on admission. The serum iron was a little below the normal range, but certainly there was no significant degree of iron deficiency. The iron-binding capacity was normal. About nine days after admission the hemoglobin had fallen from 13.5 to 10.0 gm. per 100 cc., which could be explained by the alimentary bleeding. A study of the bone marrow was obviously important, and it showed only erythroid hyperplasia.

Laparotomy was decided on after surgical consultation because of the likelihood of upper gastrointestinal bleeding. Such a decision suggests to me that the physicians and surgeons must have had in mind the presence of a remediable lesion that would justify surgical interference in a patient already very ill with cardiac failure whose prognosis was poor. The only condition I can think of is gastric ulcer. However, during preparatory blood transfusion the patient went into a state of acute circulatory failure, with evidence of acute pulmonary edema. Two days later the electrocardiogram showed first-degree atrioventricular block and left-bundle-branch block, which had developed since the tracing taken on admission. I think this indicates that she had had a myocardial infarction, which was responsible for the rapid deterioration. I think there was rapid development of uremia, precipitated by the circulatory failure, as suggested by the symptoms and the blood chemical findings. She appeared to have a terminal hypostatic pneumonia.

Dr. John F. Gibbons: In an anteroposterior projection of the chest taken on admission the heart is enlarged primarily in the region of the left ventricle, and the aorta is somewhat elongated and tortuous. I do not see any calcification within it. The lungs are clear, but the pulmonary vascular shadows are somewhat engorged and there is no fluid. Since I did not fluoroscope this patient, I cannot be definite about the indentation on the duodenum. There is a small herniation of the gastric mucosa above the diaphragm, and on the films in which we see the esophagus there is no evidence of varices. The stomach on these films seems to be of normal contour; there is nothing to suggest a neoplasm within it, nor do I see an ulceration in the wall of the stomach. The duodenal bulb apparently fills quite well, and the indentation described in the protocol refers to this defect on the inner aspect of the descending limb of the duodenum immediately distal to the bulb, which can be seen on some of the spot films. On other films the mucosa seems to be intact, and I cannot find the defect. I should like to point out an apparent defect in the immediate postbulbar area; some of the films made in various degrees of obliquity suggest the possibility of a dilated common duct crossing the duodenum. The defect described in the descending limb may or may not be significant, and if it is significant it could be due to enlarged lymph nodes in the area but I am not at all sure that it is significant. I cannot be any more positive than that.

Dr. Austin L. Vickery: Dr. DuToit, should you like to comment?

Dr. Charles H. DuToit: My main interest was whether or not the uremia preceded or followed the transfusions and pulmonary edema. We found a blood sample that had been withdrawn on or about the fifteenth hospital day, about the day when the second hemorrhage occurred. The nonprotein nitrogen on this was 150 mg. per 100 cc. That is not in the record and might throw some light on the time of development of the uremia. On the whole this patient was not in an impressive degree of congestive heart failure during most of the hospital stay. It was thought that something in the duodenum or perhaps the stomach was bleeding and might explain the slight jaundice. Also, the loss of appetite, nausea and vomiting were quite striking and quite out of proportion to the degree of congestive heart failure and persisted long after the digitalis was stopped.

Dr. McGirr: The appetite was severely impaired?

Dr. DuToit: Yes; she ate practically nothing during the hospital stay.

Dr. McGirr: That might make one think more strongly of gastric neoplasm that had not shown up.

Dr. Joseph W. Gardella: I was interested in the discussion of hemochromatosis and wondered why

it was abandoned since it seemed to fit many of the considerations brought up.

DR. MCGIRR: The pigmentation was not very pronounced in this patient; there was some doubt whether it was present at all. One would need more information about the iron content of the bone marrow and the skin. I do not think there is enough information to entitle one to make that diagnosis.

DR. FARAHE MALOOF: Did you not say that the serum iron was normal?

DR. GARDELLA: I do not think the serum iron would throw it out in the presence of persistent bleeding.

DR. BENJAMIN CASTLEMAN: The liver biopsy did not show hemochromatosis.

DR. GARDELLA: Does it always show it?

DR. CASTLEMAN: Yes.

CLINICAL DIAGNOSES

Uremia.
?Lower-nephron nephrosis.
?Nephrosclerosis.
Hypertensive cardiovascular disease.
?Recent myocardial infarction.
?Carcinoma of ampulla of Vater.

DR. EDWARD M. MCGIRR'S DIAGNOSES

Essential hypertension.
Congestive cardiac failure.
Myocardial infarction (old and terminal).
Nephrosclerosis.
Uremia.
Hypostatic pneumonia.
Bleeding from engorged gastric mucosa, as result of cardiac failure.
?Cardiac cirrhosis of liver.

ANATOMICAL DIAGNOSES

Malignant nephrosclerosis, with focal cortical infarcts.
Hypertensive heart disease, with cardiomegaly.
Pneumonitis (uremic).
(Uremia.)

PATHOLOGICAL DISCUSSION

DR. VICKERY: At autopsy we did not find a source of the bleeding in the gastrointestinal tract; there were no lesions in the entire gastrointestinal tract other than congestion and the diverticula in the sigmoid. The lungs were very congested and edematous, and microscopical examination showed a type of pneumonitis characterized by intra-alveolar edema and extravasation of red cells and mononuclear cells with occasional clumps of fibrin that is often associated with uremia and has been referred to as uremic pneumonitis. The heart was enlarged, particularly the left ventricle, weighing 430 gm. There was no evidence of an old infarct to go with the history of a coronary occlusion thirteen years previously, nor was there a recent infarct. The coronary arteries disclosed only patchy narrowing of a mild degree. The liver was enlarged and very congested and exhibited a slight degree of fatty vacuolization. The biliary tree was not remarkable.

The impressive findings were restricted to the kidneys, which were slightly less than normal in size; the right weighed 130 gm., and the left 140 gm. The cortical surfaces were quite smooth but were unusual in that they showed numerous, discrete, punctate, whitish-yellow areas that were not retracted. It was thought at the time of the autopsy that these might be microabscesses such as are seen in acute pyelonephritis. However, on microscopical study, the lesion turned out to be a malignant nephrosclerosis with a necrotizing arteriolitis affecting especially the afferent arterioles and frequently extending into the glomeruli. The vascular necrosis was of the hyaline type, extensively involving the arterial wall and without any inflammatory cellular response. A really unusual finding for a case of malignant nephrosclerosis was the presence of numerous areas of focal cortical infarction. These were apparently related to the patchy involvement of some larger arteries in the necrotizing process, with resultant thromboses. This picture of malignant nephrosclerosis was superimposed on a pre-existing benign nephrosclerosis of mild degree.

It seems in retrospect that this woman, who had a long-standing history of hypertension, had come into the hospital presumably with congestive heart failure; for some unknown reason a fulminant malignant nephrosclerosis, which terminated in uremia and death in only a few days, was precipitated. The histologic appearance of areas of infarction in the kidneys and the arterial lesions themselves were indicative only of a few days' duration and certainly could not have been present on admission almost three weeks previously.

We can only speculate about the hematemesis. The last hematemesis four days before death may have been caused by gastrointestinal congestion due to relative congestive heart failure or by the sudden onset of uremia. As Dr. DuToit mentioned, the nonprotein nitrogen at that time was 150 mg. per 100 cc., and I think the bleeding could have been on the basis of an uremic upper enteritis, but this can only be speculated upon. Whatever the cause, the bleeding site could well have healed in the four days before death.

DR. MALOOF: Were the adrenal glands normal?

DR. VICKERY: They were not unusual.

CASE 40482

Presentation of Case

A seventy-three-year-old Italian entered the hospital because of anorexia.

Four weeks previously he noted anorexia and postprandial distress, with associated malaise and change in bowel habits. On the day before admission, he had a shaking chill and a temperature of 101°F. At that time the urine was found to be darker than normal. His family physician referred him to the Emergency Ward. There was no history of venipuncture, transfusions, tuberculosis, raw-milk ingestion or contact with jaundiced persons. He reported an 11-pound weight loss since the preceding year.

The temperature was 101.4°F., the pulse 100, and the respirations 20. The blood pressure was 105 systolic, 60 diastolic.

Physical examination revealed a cachectic, icteric, aged, lethargic man. There was vitiligo of both hands, but no pigmentation of palmar creases or spider angiomas. A diffuse, shotty cervical and axillary adenopathy was present. The chest was emphysematous, and the heart borders could not be percussed. The heart rate was 100, with occasional premature beats; no murmurs were heard. The abdomen was soft, and no masses or tenderness were elicited. The spleen was not palpable. The upper border of liver dullness was at the sixth intercostal space, and a smooth liver edge was felt 1 fingerbreadth below the right costal margin. Rectal examination was not remarkable.

Urinalysis showed amber, clear urine, with a positive Harrison spot test for bile, acid reaction, a specific gravity of 1.018, a ++ test for albumin, no reducing substances, and 4 to 7 white cells, 4 to 5 red cells and occasional granular casts per high-power field in the sediment. Examination of the blood revealed a hemoglobin of 7.5 gm. per 100 cc., a white-cell count of 8000 and a smear showing relative monocytosis of 16 per cent of cells counted. The red cells were anisocytotic, and a number of target cells were noted. The blood Hinton test was negative. The serum bilirubin was 3.5 mg. total, and 2.5 mg. direct, the serum nonprotein nitrogen 32 mg., the albumin 3.3 gm., the globulin 1.8 gm. (albumin-globulin ratio of 1.8), the alkaline phosphatase 25 units, the cholesterol 99.6 mg., the cholesterol esters 16.4 mg., and the serum iron 85 microgm. (normal, 125 to 200 microgm.) per 100 cc., with a total iron-binding capacity of 30 per cent; the sodium was 124 milliequiv. per liter. The prothrombin time was 18 seconds (normal, 13 seconds), or 31 per cent of normal. The cephalin flocculation was + in twenty-four and ++ in forty-eight hours. A Coombs test was negative. The red cells demonstrated a decreased osmotic fragility. The serum was negative for heterophil-antibody and brucella agglutinins. Two blood cultures showed no growth. The urinary urobilinogen was 1.54 Ehrlich units. A cytologic examination of gastric aspirate was negative for tumor cells. Three stool specimens were negative for occult blood. A stool culture was negative for pathogens. A roentgenogram of the chest disclosed mottled areas of increased density in the right upper lobe interpreted as a chronic inflammatory process. An upper gastrointestinal series revealed no abnormality. A barium-enema examination showed ileus and suggestive evidence of an incomplete obstruction in the proximal sigmoid without a demonstrable lesion.

The patient's course was initially febrile, with daily elevations of oral temperature of 103 to 104°F. He was treated first with parenteral injections of vitamin K preparation without improvement in the prothrombin time. On the twelfth hospital day he had a shaking chill, with lethargy and mental confusion. On the next day, abdominal distention appeared, and a plain film of the abdomen showed gas-filled large bowel. Sigmoidoscopy to a distance of 50 cm. revealed no abnormality. On the thirteenth hospital day 1000 cc. of whole blood was given, with an increase in the hemoglobin to 10 gm. per 100 cc. Penicillin, 2,400,000 units daily, and streptomycin, 0.5 gm. daily, were started on the fourteenth hospital day, by which time the temperature had already returned to normal. The patient became progressively more confused, deteriorated rapidly and died on the seventeenth hospital day, after two days of hypothermia, hypotension and oliguria.

Differential Diagnosis

Dr. Leonard W. Cronkhite, Jr.*: Briefly, this was an acute febrile disease of about seventeen days' duration preceded by four weeks of prodromal signs characterized by anorexia, postprandial distress and malaise and followed by dark urine, fever and shaking chills. The patient was described as cachectic, suggesting that the process had been present for longer than the four weeks reported.

Since there were abnormal x-ray findings in the lungs and in the colon I think it would be worth while to look at the films first.

Dr. Stanley M. Wyman: In the chest there is a patchy process involving chiefly the apexes of the lungs, the right more than the left. The general emphysema of the chest is well seen on the lateral view. In the second chest film, taken about two weeks later, the diaphragm is higher, but no areas of significant infiltration are present. The films of the abdomen show a great deal of gas in the colon and in loops of small bowel but no gross dilatation of large or small intestines. The films of the upper gastrointestinal series demonstrate nothing remarkable except a hiatus hernia. The second of two examinations of the colon, although far from ideal, fails to outline any gross lesion. I think all that one can say is that there was no obstruction to retrograde flow of barium and no obvious gross filling defect.

Dr. Cronkhite: While this patient was in the hospital he continued to run a spiking temperature.

*Clinical assistant in medicine, Massachusetts General Hospital.

The temperature chart, which was just passed to me, is not as spiking as I had thought, but the temperature was high throughout the hospital stay until the terminal forty-eight hours.

The protocol deals with a large mass of laboratory data, which is like a bequest of confederate money: there is a great deal of it, but it is not very useful. I might look at the hematologic data first. There was a profound anemia, — hemoglobin of 7.5 gm. per 100 cc., — and the red cells were described as showing marked anisocytosis, with target cells noted. Somebody apparently suspected Cooley's trait and did a fragility test, which showed a decrease in osmotic fragility. Those observations are perfectly consistent with Cooley's trait, or thalassemia minor, but I am sure that they have no real bearing on the major disease. The serum iron values are not low enough to enable one to say that there was an iron deficiency and not high enough to indicate acute massive hemolysis. They were in the range of the anemia that one sees with chronic wasting disease or chronic sepsis. The Coombs test was negative, and three stools were negative for occult blood. I can say only that the patient had a profound anemia that was probably not caused by blood loss or massive hemolysis — that it was not primary iron deficiency but was of the nonspecific type, which accompanies severe wasting disease with or without sepsis.

The total white-cell count was 8000, and there was an increase in the number of monocytes to 16 per cent. A relative monocytosis, it is generally agreed, is a nonspecific reaction to a number of infections. One usually thinks of tuberculosis since the tubercle bacillus is supposed to cause a monocytic response. This monocytosis can also happen in infectious hepatitis, in which there are large vacuole-filled mononuclear cells, and in syphilis, typhoid fever, brucellosis, Hodgkin's disease and many others so that it is really not a helpful bit of information.

The liver-function tests are of considerable interest. The degree of icterus was mild. The initial titer was apparently 3.5 mg. per 100 cc. of total bilirubin. No further values were given so that I am not sure whether the patient became more and more jaundiced. There was bile in the urine and slightly elevated urinary urobilinogen. Of the remainder of the tests, because they contradict one another, I must ignore some and accept others. The alkaline phosphatase was strikingly elevated; on the other hand the cholesterol and the cholesterol esters were markedly depressed. The alkaline phosphatase leads me to think of an obstructive phenomenon, and the very low cholesterol and cholesterol esters of severe hepatocellular disease. The prothrombin time was prolonged to 18 seconds, with a normal value of 13 seconds, and did not respond to vitamin K. This, too, makes me suspect the presence of primary hepatocellular disease. The cephalin flocculation was equivocal — + in twenty-four and ++ in forty-eight hours. The albumin and globulin were not sufficiently out of order to be conclusive. I have either to accept the evidence in favor of hepatocellular disease and discard the alkaline phosphatase or to accept the alkaline phosphatase and assert that the hepatocellular disease was a secondary phenomenon. I believe that a very low cholesterol and cholesterol ester would be most unusual in pure obstructive jaundice and shall say that the alkaline phosphatase can be explained as a secondary phenomenon. In an elderly man one must always consider Paget's disease in a bone that is not visualized in the x-ray film. I shall choose to interpret this as severe hepatocellular disease with a secondary obstructive phenomenon.

The normal nonprotein nitrogen, with the ++ test for albumin and the bile in the urine, together with the cells and casts in the urinary sediment, are more than one can explain on the basis of hypotension in an elderly man. I must assume that there was some sort of active process in the kidneys. Other tests such as the blood and stool cultures, the brucella agglutinations and the Papanicolaou smear of the stomach aspirate are helpful in a negative fashion.

When I read over the protocol I thought of a neoplasm. The x-ray report as written in the protocol is misleading because it suggests that there was a partially obstructing lesion in the colon. I choose to disregard this on the basis of the severe degree of hepatocellular damage with a smooth liver, the lack of overt physical findings of a metastatic or primary cancer in the large bowel and the guaiac-negative stool. Other neoplasms such as the lymphoma-Hodgkin group, which we have to consider in obscure cases of fever and cachexia, I shall disregard on the basis of lack of evidence with full realization that it may well have been one of these.

Miliary tuberculosis is certainly a consideration in anyone who has a disease characterized by cachexia, fever, a fairly prolonged course and involvement of multiple organs. It would be most unusual, however, for a miliary process in the liver to be so severe as to interfere with the prothrombin time, the cholesterol, cholesterol esters and other liver-function tests.

There was no evidence of toxic hepatitis, and I do not think it is worth while discussing that further.

In a jaundiced patient with renal involvement and an acute febrile reaction one must always consider the possibility of the leptospiral infections. I have been impressed, in reading over the case histories of patients with leptospiral disease, by the great variation in the severity and duration of symptoms. There is variation in the degree of hepatic and of renal involvement. In an occasional case there is hemorrhagic pulmonary involvement. I do not think one can make that diagnosis clinically unless there is a history of exposure to rats and perhaps the presence of a skin rash and conjunctivitis. Without a definite agglutination test, I think one can only mention it in passing.

Infection of the biliary tree in the liver would perhaps fit some of these liver-function studies. There is very little to go on to rule it either in or out.

Infectious hepatitis, I judge, was considered in this elderly man because he had a four-week period of

anorexia and malaise, followed by jaundice, fever and a progressive downhill course. The liver-function tests were not altogether consistent with this since the cephalin flocculation was equivocal.

In passing I might mention another diagnosis. At another clinicopathological conference I happened to see a case of spontaneous thrombosis of the hepatic artery with a clinical picture similar to this. That patient had severe vascular disease and apparently a piece of an aortic thrombus broke off and lodged in the area of the celiac axis. A thrombus was slowly propagated up into the liver. He became progressively more jaundiced, and liver function was deranged. He was explored and finally died in liver failure, which I judge was the mode of death of the patient under discussion.

Having mentioned these half-a-dozen or so entities, I am forced to commit myself to a definite diagnosis; I cannot honestly make a definite diagnosis. I am forced to say that the patient had a chronic disease, with either an acute exacerbation or a superimposed acute disease. The first diagnosis I shall make will be one about which the pathologists have difficulty in arguing — namely Cooley's trait, which had no relation to the major problem. I prefer to take Dr. Wyman's interpretation of the pulmonary lesion and say that it was an old inactive process probably not related to the major problem. I shall label that an old tuberculous process in the apexes of both lungs, perhaps more severe on the right. I think the patient had a renal infection that was probably chronic and preceded the liver involvement — a subacute pyelonephritis. I shall make the more conservative diagnosis of the liver disease and call it infectious hepatitis. The anemia, I think, was of the type seen with chronic wasting disease and infection.

DR. FARAHE MALOOF: Is it true that on the fourteenth hospital day, before antibiotics were started, the temperature returned to normal?

DR. AUSTIN L. VICKERY: Yes; it came down, and then antibiotics were started.

DR. ALFRED KRANES: Did the patient become progressively more jaundiced while he was in the hospital?

DR. HERSCHEL D. COLLINS: Yes.

DR. BENJAMIN CASTLEMAN: Dr. Kranes, what would your diagnosis be?

DR. KRANES: I should be inclined to agree with Dr. Cronkhite that this patient had an acute or a subacute liver condition.

DR. JOHN D. STOECKLE: Does Dr. Cronkhite think that the fever and course are compatible with infectious hepatitis?

DR. CRONKHITE: I felt constrained to postulate two diseases. I think he had a renal infection in addition to the infectious hepatitis.

CLINICAL DIAGNOSES

Liver failure.
Metastatic cancer to liver.
Anemia.

DR. LEONARD W. CRONKHITE, JR.'S, DIAGNOSES

Infectious hepatitis.
Pyelonephritis.
Secondary anemia.
Inactive apical tuberculosis.
Cooley's trait.

ANATOMICAL DIAGNOSES

Malignant lymphoma, Hodgkin type, involving liver, spleen and mesenteric, retroperitoneal, axillary, porta-hepatic and supraclavicular lymph nodes.
Jaundice.
Ascites.
Pulmonary congestion and edema, mild.
Pulmonary emphysema, right.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Grossly, the liver was covered with numerous yellow-white nodules, 4 or 5 mm. in diameter, between which were many tiny ones. Similar nodules were found throughout the liver. The spleen showed exactly the same picture, the so-called suet-like foci that one sees in Hodgkin's disease. Microscopically, there was extensive miliary spread of Hodgkin's disease. The liver cells between the foci did not look too abnormal, but I think the widespread replacement of the liver cells by the disease accounted for the jaundice and liver failure. The lymph nodes throughout the body were enlarged up to 2 cm. in diameter, and these as well as the shotty lymph nodes in the axilla proved to be involved with Hodgkin's disease. One lymph node about 2 cm. in diameter was close to the common bile duct; however, we were able to get a free flow of bile down the common duct. It is conceivable that that node caused partial obstruction to the common bile duct that might have added to the liver impairment.

The kidneys gave no evidence of infection. The lungs were edematous.

DR. MALOOF: What was the trouble in the apexes of the lungs?

DR. CASTLEMAN: That was old tuberculous scarring, but nothing active. We found nothing in the large bowel to account for the obstruction.

DR. EDWARD B. BENEDICT: Was a needle biopsy of the liver done?

DR. CASTLEMAN: No; a needle biopsy here would certainly have shown the disease. In 2 or 3 cases of Hodgkin's disease the needle biopsy has made the diagnosis.

DR. BENEDICT: I was asked about peritoneoscopy, which would have helped and was actually scheduled, but the patient became rapidly worse and peritoneoscopy was canceled.

DR. MALOOF: Would a biopsy of a lymph node have shown the disease?

DR. CASTLEMAN: I believe so.

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

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THE GENERAL WELFARE

REGARDLESS of its apparent effect on the recent election, or the lack of it, general prosperity seems to have been an earmark of the present administration. It is a prosperity of the luxuries of life; a deep-freeze, air-conditioned prosperity characterized by a leafless forest of television antennae; a bumper-to-bumper prosperity in which the earth groans because of its lack of space in which to park the products of automotive conception.

These conditions, impermanent as they are, are such that a people devoted to material things is inclined more and more to rely on its government — regardless of the party in power — to guarantee a security capable of banishing practically all hardships except that personally remote one attendant on an eventual demise. They are conditions that do not at the moment inspire a dreadful anxiety over things that may not happen; consequently, although the expected social-security handout is complacently awaited, such less tangible benefits as a health reinsurance plan do not stir the voters deeply, especially since most of them do not know what it is all about.

Almost as if there were a relation between the two the announcement of a prolonged-illness certificate to be issued by Massachusetts Blue Cross and Blue Shield has been followed by a statement from Mrs. Hobby regarding the health legislation on which her department will concentrate in the next Congress. The social-security structure, according to Mrs. Hobby, has been expanded almost to the limits of its possible coverage; within hours President Eisenhower had announced his intention of resubmitting the health reinsurance plan at the next session of Congress.

This bill, according to the Secretary of Health, Education and Welfare, whose department has been responsible for its drafting, will be "clearer and better" than the one that was defeated this year. The President himself is responsible for the statements that it will be "an important part of a health program in the great gaps in the field of health" and that " we are years behind our potential achievement in the availability and adequacy of health services."

Mr. Nelson Rockefeller, undersecretary of the department headed by Mrs. Hobby, in giving the Administration's plans a hand, distinguished sharply between "the liberty-eroding concept of an ever-expanding 'welfare state' " and the " general welfare" of the people as sanctioned by the Constitution. The point requires a fine definition, but it is difficult to see wherein may lie the dangers attributed to health reinsurance, or indeed what there is about it that makes it a *cause célèbre*. The American Medical Association holds three counts against it — that it is unnecessary, that it holds out false promises and that it introduces the federal Government into an area where it does not properly belong.

Holding no brief for the introduction of govern-

ment into any form of medical practice whatsoever, one may still wonder where the functional limits of a government of, for and by the people may lie. Are they not where a majority of the people wish or suffer them to be?

In this respect it is interesting to learn from a special report of the Washington Office of the American Medical Association that the expenses of the federal Government for its health, medical and related activities have gone this fiscal year from $1,775,882,000 to $2,141,681,661.

THE WILLIAM OSLER MEDAL

To stimulate interest and research in medical history among students of the medical schools of the United States and Canada, the American Association of the History of Medicine established in 1940 a medal to be granted annually to the author of the best student essay submitted to the Association. The

The William Osler Medal
(Three-Quarters Actual Size)

medal, in bronze, carries a profile portrait of Osler, drafted by Dr. Adolph H. Schultz, professor of physical anthropology at Johns Hopkins University, with appropriate symbols of medicine and Osler's name and that of the Association. It was first awarded to John T. Barrett, of Boston University School of Medicine, in 1942 for his essay, "The Inoculation Controversy in Puritan New England," a fresh and stimulating re-evaluation of an old subject, and in the subsequent years other papers of worth have been granted the prize. The latest award was to Robert J. T. Joy, a senior medical student at Yale University School of Medicine, in 1954 for his original paper entitled "The Natural Bonesetters, with Special Reference to the Sweet Family of Rhode Island: A study of an early phase of orthopedics." Two other students received honorable mention with a yearly subscription to the *Bulletin of the American Association of the History of Medicine,* in which the student essays are published.

For 1955 the William Osler Medal Committee will consider unpublished essays by men or women who were students in schools of medicine and had not yet obtained their doctor's degree at the time the essay was written. Essays should not exceed 10,000 words in length and must be submitted to Lloyd G. Stevenson, M.D., Faculty of Medicine, McGill University, 3640 University Street, Montreal, Canada, by March 1.

The Committee has prepared some points of guidance for the novitiates who will compete for the medal, but the advice provided is pertinent to almost all medical writing, by amateurs or professionals, and will warm the hearts of all editors of medical journals. Dr. Stevenson and his committee, consisting of Wilburt C. Davison, of Durham, North Carolina, Joseph H. Pratt, of Boston, and Ilza Veith, of Chicago, warn the amateur that his temptation will be "to belabor again the well labored subjects; to rewrite the biographies of the well-known, and to retell the tales told long since."

It must instead be his purpose to pursue the distinct quality of originality, not confusing it with "brilliance, profundity and great magnitude." For originality has a value of its own, accessible to all who would seek it, and the student should without too great difficulty find for his pen a subject that "has not yet been sufficiently elucidated."

The instructions of the Committee form in fact a brief and brilliant essay in themselves; a short homily on historical research and intellectual curiosity in matters historical, under the terms of the Osler Medal. The final advice is a rare bit of philosophy: "To reassess common and well established interpretations usually requires more experience and knowledge than is likely in the novitiate. Originality where others have already labored is not to be sought lightly, but where attainable it is a worthwhile goal."

GENERAL PRACTITIONER OF THE YEAR

In his letter to the Board of Trustees of the American Medical Association submitting the name of Dr. Harvey A. Kelly, of Winthrop, as the Massachusetts nominee for the General Practitioner of the Year, Dr. Curtis C. Tripp, president of the Massachusetts Medical Society made the following statement:

> We who have worked with Harvey find it difficult to describe him in terms of one man for he literally does the work of two men. These "two Dr. Kelly's" are a credit to American medicine.
>
> One Dr. Kelly is the traditionally dedicated General Practitioner devoted to the care of his patients, intent on always providing them with the latest and best in medical care and treatment. He has kept abreast of medicine during his near half-century of practice by attending — and in many instances establishing, postgraduate medical courses. And he has been instrumental in the expanding and improving of medical facilities in his community.
>
> The other Dr. Kelly is the physician dedicated to the improvement of the medical profession as a whole. He has

worked tirelessly and effectively on medical society matters, serving as a Councilor for twenty years, president of his district medical society, vice-president of the State Society, and committee chairman. He is one of the organizers and a past president of the Massachusetts Academy of General Practice.

Dr. Kelly richly deserves the American Medical Association's General Practitioner of the Year award. We of the Massachusetts Medical Society heartily endorse his nomination.

The *Journal* seconds the nomination of Dr. Kelly with equal heartiness. As a member of the Editorial Board, he has won its esteem not only for his sound advice on matters medical but also for the qualities of friendliness, human understanding and genuine kindness that mark a man for true distinction.

CHRISTMAS SEALS AND CONTROL OF TUBERCULOSIS

On November 22 the National Tuberculosis Association opened the annual sale of Christmas Seals. This campaign, which will continue through December, marks the forty-eighth in a series of appeals for support of the Association and its 3000 affiliated organizations, which depend entirely on the proceeds of these sales. Early this year the Association itself celebrated its fiftieth anniversary, an event already referred to in these columns.*

The half-century of the Association's existence is one of notable progress in the control of tuberculosis, the purpose for which it was established, but the gains achieved do not justify any relaxing of effort so long as this disease, once the leading cause of death, remains a menace to the health, happiness and prosperity of millions. Thus, although the death rate has been reduced by approximately 50 per cent, tuberculosis constitutes the gravest public-health problem in the United States and the most serious infectious-disease problem in the world. Prevention through case finding, health education, medical research and rehabilitation is the major step toward the eventual goal of complete eradication; cure and prevention are both possible, but both depend on constant investigation, which in turn receives tremendous help from the voluntary tuberculosis associations.

It is more than coincidence that the fifty years of greatest progress in control occurred during the period since the foundation of the National Tuberculosis Association. The past record and plans for future advances justify the expectation that the forty-eighth sale of Christmas Seals will meet with the same generous response given its predecessors. The health of the public will ultimately be the gainer.

*Editorial. Golden anniversary. *New Eng. J. Med.* **250**:617, 1954.

Asylum for Inebriates. — *There is a strong probability that an asylum for the reception and treatment of confirmed drunkards will at last be instituted in this country.*

Boston M. & S. J., *Dec. 6, 1854*

NOTICES

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The House Officers' Association of the Boston City Hospital announces the schedule of the Tuesday evening lecture series, to be held in the New Cheever Amphitheater, Dowling Building, Boston City Hospital, at 7 p.m., as follows:

December 7. Infectious Syndromes of the Liver and Subphrenic Space. Dr. Harold Jeghers, Georgetown University Hospital.

December 14. The Physiology of Gastric Secretion as Related to Peptic Ulcer. Dr. Lester R. Dragstedt, University of Chicago, The School of Medicine.

December 21. Constipation and Its Management. Dr. Franz J. Ingelfinger, Boston University School of Medicine.

SOCIETY MEETINGS AND CONFERENCES

DECEMBER, 1954–APRIL, 1955. Postgraduate Medical Institute. Page 451, issue of September 9.

DECEMBER, 1954–MAY, 1955. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

DECEMBER 2–29. Consultation Clinics for Crippled Children in Massachusetts. Page 918, issue of November 25.

DECEMBER 3. New England Society of Anesthesiologists. Page 876, issue of November 18.

DECEMBER 3. New England Rheumatism Society. Page 875, issue of November 18.

DECEMBER 3, 1954–MARCH 25, 1955. Postgraduate Course in Occupational Medicine. Page 922, issue of November 25.

DECEMBER 4–9. American Academy of Dermatology and Syphilology. Page 876, issue of November 18.

DECEMBER 4, 1954–MAY 7, 1955. Middlesex South District Medical Society, Postgraduate Course. Page 758, issue of October 28.

DECEMBER 5. American Academy of Dental Medicine. Page 1092, issue of June 24.

DECEMBER 6, 1954–JANUARY 17, 1955. Hartford Medical Society. Page 496, issue of September 16.

DECEMBER 7. Medical Television Program. The Doctor. (Cavalcade of America.) Page 631, issue of October 7.

DECEMBER 7, 14 and 21. House Officers' Association. Boston City Hospital. Notice above.

DECEMBER 8. New England Pediatric Society. Page 921, issue of November 25.

DECEMBER 8. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

DECEMBER 8 and 9. Myasthenia Gravis Foundation Conference. Page 834, issue of November 11.

DECEMBER 13–17. Congress of Obstetrics and Gynecology. Page 748, issue of April 29.

DECEMBER 14. New York Society for Circulatory Diseases. Page 921, issue of November 25.

JANUARY 3–MAY 9, 1955. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

JANUARY 10–15. Course in Care of Atomic Casualties. Page 285, issue of August 12.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, DECEMBER 9

THURSDAY, DECEMBER 9

*8:00 p.m. House Officers' Night. Invited Guest Speakers. Lecture Hall, Carney Hospital.

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building. Children's Medical Center, 35 Binney Street.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m. Thoracic Conference. Tumors of the Lung. Dr. Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*12:00 m.–1:00 p.m. Plasma Fractionation and Clinical Products Therefrom. Dr. James L. Tullis. Stearns Auditorium, New England Center Hospital.

*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

(Concluded on page xxvi)